

Today's hypertensives
with new concerns...



THE CARDURA GENERATION

Choose **CARDURA**: first-line therapy
for a new generation of hypertensives.

— Choose **CARDURA** for around-the-clock blood pressure control that doesn't jeopardize blood lipids or blood sugar.¹⁻³

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than with placebo: dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA® 

(doxazosin mesylate) Scored Tablets
1 mg, 2 mg, 4 mg, 8 mg

Please see brief summary of prescribing
information on next page.
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HYPERTENSION CONTROL FOR A NEW GENERATION.

ONCE-A-DAY
CARDURA[®]
 (doxazosin mesylate) Scored Tablets
 1 mg, 2 mg, 4 mg, 8 mg

CARDURA[®] (doxazosin mesylate) Tablets

Brief Summary of Prescribing Information
INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution. Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group. Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncope and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory Test Interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg/day about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-¹⁴C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 48% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
SKIN APPENDAGES:	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N. S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%

References: 1. Pickering TG, Hypertension and Lipid Trial Study Group. The use of 24-hour ambulatory monitoring in the assessment of antihypertensive therapy. Presented at the American Academy of Family Physicians 43rd Annual Assembly; September 24-29, 1991; Washington, D.C. 2. The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. Arch Intern Med. 1991;151:1413-1423. 3. Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. Curr Ther Res. 1990;47:278-284.

		DOXAZOSIN (N=339)	PLACEBO (N=336)
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturition Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hyposthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. **Cardiovascular System:** angina pectoris, myocardial infarction, cerebrovascular accident; **Autonomic Nervous System:** pallor; **Metabolic:** thirst, gout, hypokalemia; **Hematopoietic/lymphadenopathy:** purpura; **Reproductive System:** breast pain; **Skin Disorders:** alopecia, dry skin, eczema; **Central Nervous System:** paresis, tremor, twitching, confusion, migraine, impaired concentration; **Psychiatric:** paranoia, amnesia, emotional lability, abnormal thinking, depersonalization; **Special Senses:** parosmia, earache, taste perversion, photophobia, abnormal lacrimation; **Gastrointestinal System:** increased appetite, anorexia, fecal incontinence, gastroenteritis; **Respiratory System:** bronchospasm, sinusitis, coughing, pharyngitis; **Urinary System:** renal calculus; **General Body System:** not flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

No data are available in regard to overdosage in humans.

The oral LD₅₀ of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA[®] TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets. Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66). Recommended Storage: Store below 86°F (30°C).

CAUTION: Federal law prohibits dispensing without prescription.

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References: 1. Levy B, Rosenberg LN, Colasante DA. A comparison of VERELAN® and Procordia® XL in the treatment of patients with mild to moderate hypertension. American College of Clinical Pharmacology. 21st Annual Meeting, 1992. Abstract. 2. Further analysis of Levy B, et al. (See reference 1.) Data on file. Lederle Laboratories. Pearl River, NY.

Brief Summary

VERELAN®
Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdose. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing), dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk, therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (2.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR <50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris; atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.



Manufactured for
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American Cyanamid Company
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by ELAN PHARMACEUTICAL RESEARCH CORP.
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VERELAN

AS EFFECTIVE AS PROCARDIA XL[®] IN REDUCING BP AT THE 24TH HOUR^{1,2}

Reduction in mean DBP measured 24±2 hours after dosing



Results of a 12-week, randomized, double-blind, parallel, comparative study of patients with mild-to-moderate hypertension in 10 study sites nationwide. Patients not controlled on VERELAN 240 mg/day were titrated to 360 mg/day and, if needed, 480 mg/day; patients not controlled on Procardia XL 30 mg/day were titrated to 60 mg/day and, if needed, 90 mg/day. There was no significant difference between groups in the number of titrations to goal DBP (<90 mm Hg).

*Procardia XL is a registered trademark of Pfizer Inc.

Constipation, which can easily be managed in most patients, is the most frequently reported side effect of verapamil.

Please see brief summary of Prescribing Information on adjacent page.

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240 mg
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*Barbara Gerbert, PhD;
Thomas Bleecker, PhD; Jane Bernzweig, PhD*

Commentary: 55

**Reflections After 9 Years of Working
With Patients With Acquired
Immunodeficiency Syndrome:
What I Have Learned**

Kay A. Bauman, MD, MPH

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see Warnings), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents.

Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecostasia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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Please see references and brief summary on adjacent page.

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BuSpar[®] (buspirone HCl)

References: 1. Data on file, Bristol-Myers Squibb Company. 2. Cohn JH, Bowden CL, Fisher JG, Rodos JJ. Double-blind comparison of buspirone and clonazepam in anxious outpatients with or without depressive symptoms. *Psychopharmacology*. 1992;25:10-21. 3. Feighner JP, Cohn JH. Analysis of individual symptoms in generalized anxiety—a pooled, multisite, double-blind evaluation of buspirone. *Neuropsychopharmacology*. 1989;21:124-130. 4. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med*. 1987;82(suppl 3A):20-26. 5. Newton RE, Marunycz JJ, Alford CE III, Napoliello MJ. Review of the side-effect profile of buspirone. *Am J Med*. 1986;80(suppl 3B):17-21.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: **General—Interference with cognitive and motor performance:** Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdrawal patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally even as seizure.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine-mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less tightly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): Commonly Observed—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: **Cardiovascular:** Tachycardia/palpitations 1%. **CNS:** Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. **EENT:** Blurred vision 2%. **Gastrointestinal:** Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. **Musculoskeletal:** Musculoskeletal aches/pains 1%. **Neurological:** Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. **Skin:** Skin rash 1%. **Miscellaneous:** Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. **Cardiovascular—**frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. **Central Nervous System—**frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. **EENT—**frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. **Endocrine—**rare: galactorrhea, thyroid abnormality. **Gastrointestinal—**infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. **Genitourinary—**infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. **Musculoskeletal—**infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. **Neurological—**infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. **Respiratory—**infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. **Sexual Function—**infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. **Skin—**infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. **Clinical Laboratory—**infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. **Miscellaneous—**infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: Controlled Substance Class—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: Signs and Symptoms—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdosage Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialysis of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.
U.S. Patent Nos. 3,717,634 and 4,182,763

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Cognitive Therapy and Pharmacotherapy for Depression: Singly and in Combination

Cognitive therapy and imipramine hydrochloride tricyclic pharmacotherapy, each singly and in combination, were compared in the treatment of non-psychotic, nonbipolar depressed outpatients. One hundred seven patients were randomly assigned to 12 weeks of active treatment; 64 patients completed the full course of treatment. Rates of attrition were high but not differential. Cognitive therapy and pharmacotherapy did not differ in terms of symptomatic response, either in the primary analyses or in secondary analyses restricted to more severely depressed outpatients. Initial severity did predict response within pharmacotherapy alone, but not within cognitive therapy. Combining cognitive therapy with pharmacotherapy did not markedly improve response over that observed for either modality alone, although such nonsignificant differences as were evident did favor the combined treatment. Two patients died as a consequence of suicide attempts, both of which involved study medication.

(1992;49:774-781) Steven D. Hollon et al, Department of Psychology, Vanderbilt University, 306 Wilson Hall, Nashville, TN 37240.

ARCHIVES OF INTERNAL MEDICINE

Systolic Hypertension in the Elderly: Pathophysiology and Management

Isolated systolic hypertension occurs with increased prevalence in the elderly population. It is characterized by reduced vascular compliance, often combined with increased peripheral resistance. These changes are not specific to patients with systolic hypertension, occurring, perhaps to a lesser extent, in the normotensive aging population as well. Systolic hypertension is associated with a risk of cardiovascular morbidity and mortality that possibly exceeds that associated with systolic-diastolic hypertension. However, until the recent report of the Systolic Hypertension in the Elderly Program, the benefit of treatment of this population was undocumented. The Systolic Hypertension in the Elderly Program demonstrated that lowering of blood pressure with a diuretic, combined, when necessary, with a beta blocker, reduced the rate of myocardial infarction and stroke. Other agents may also be effective in lowering blood pressure, although their ability to reduce cardiovascular morbidity and mortality in this population remains to be documented. The results suggest that pharmacologic treatment be considered for patients older than 60 years whose

Continued on page 16

IN CONCERT

A safety profile that works in concert with other antihypertensive agents

In limited controlled trials, no notable change in the nature or frequency of adverse reactions was shown when LOZOL was combined with other antihypertensives. LOZOL is well tolerated and does not adversely affect lipids.¹⁻⁴ And unlike Dyazide* or Maxzide,[†] there may be no increased risk of hyperkalemia when LOZOL is used in combination with ACE inhibitors.

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* Dyazide (triamterene-hydrochlorothiazide), a potassium-sparing diuretic, is a registered trademark of SmithKline Beecham Pharmaceuticals.

† Maxzide (triamterene-hydrochlorothiazide), a potassium-sparing diuretic, is a registered trademark of Lederle Laboratories. Please see brief summary of prescribing information below.

LOZOL® (indapamide) 2.5 mg tablets

BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure. *Usage in Pregnancy:* See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (see ADVERSE REACTIONS, hypokalemia), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability. Distal hypomagnesemia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease). Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically. Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed. Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine. In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical trials, adverse reactions with $\geq 5\%$ cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; $< 5\%$ cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Hypokalemia with concomitant clinical signs or symptoms occurred in 3% of patients receiving indapamide 2.5 mg q.d. and 7% of patients receiving indapamide 5 mg q.d. In long-term controlled clinical trials comparing the hypokalemic effects of daily doses of indapamide and hydrochlorothiazide, however, 47% of patients receiving indapamide 2.5 mg, 72% of patients receiving indapamide 5 mg, and 44% of patients receiving hydrochlorothiazide 50 mg had at least one potassium value (out of a total of 11 taken during the study) below 3.5 mEq/L. On the indapamide 2.5 mg group, over

50% of those patients returned to normal serum potassium values without intervention. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep tightly closed. Store at room temperature. Avoid excessive heat. Dispense in tight containers as defined in USP. See product circular for full prescribing information. Revised: March 1992.

References: 1. Beling S, Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983;106(1, Part 2):258-262. 2. Meyer-Sabellek W, Gotzen R, Heltz J, et al: Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension* 1985;7(Suppl III):170-174. 3. Horgan JH, O'Donovan A, Teo KK: Echocardiographic evaluation of left ventricular function in patients showing an antihypertensive and biochemical response to indapamide. *Postgrad Med J* 1981; 57(Suppl 2):64-67. 4. Scalabrino A, Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35(1):17-22.

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- The 8th most frequently prescribed medication in America.²

vicodin ES

(hydrocodone bitartrate 7.5mg [Warning: May be habit forming]
and acetaminophen 750mg)

**Extra strength pain relief
you can phone in.**

¹ Data on file, Knoll Pharmaceutical Company

² Standard industry new prescription audit.

* (hydrocodone bitartrate 5mg [Warning: May be habit forming] and acetaminophen 500 mg)



Maintain control of your patient's pain therapy.

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*Do not
substitute*

vicodin ES

(hydrocodone bitartrate 7.5mg (Warning: May be habit forming)
and acetaminophen 750mg)

It's your prescription— not a suggestion.

INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain. **CONTRAINDICATIONS:** Hypersensitivity to acetaminophen or hydrocodone. **WARNINGS: Respiratory Depression:** At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression. **Head Injury and Increased Intracranial Pressure:** The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. **Acute Abdominal Conditions:** The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions. **PRECAUTIONS: Special Risk Patients:** VICODIN/VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. **Cough Reflex:** Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when VICODIN/VICODIN ES Tablets are used postoperatively and in patients with pulmonary disease. **Drug Interactions:** Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with VICODIN/VICODIN ES Tablets may exhibit an additive CNS depression. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus. **Use in Pregnancy: Teratogenic Effects:** Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN/VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic effects:** Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. **Labor and Delivery:** Administration of VICODIN/VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN/VICODIN ES Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include: **Central Nervous System:** Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence and mood changes. **Gastrointestinal System:** The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN/VICODIN ES Tablets may produce constipation. **Genitourinary System:** Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported. **Respiratory Depression:** Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated. **DRUG ABUSE AND DEPENDENCE:** VICODIN/VICODIN ES Tablets are subject to the Federal Controlled Substance Act (Schedule III). Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN/VICODIN ES Tablets should be prescribed and administered with caution. **OVERDOSAGE: Acetaminophen Signs and Symptoms:** In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. **Hydrocodone Signs and Symptoms:** Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Revised March 1992

5890

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Williams & Wilkins 428 East Preston Street, Baltimore, MD 21202

Ismo® (isosorbide mononitrate) 20 mg tablets

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR.)

Indications and Usage Ismo is indicated for prevention of angina pectoris due to coronary artery disease. The onset of action is not rapid enough for it to be useful in aborting an acute anginal episode.

Clinical Pharmacology Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate comes from the mononitrate. Ismo is not subject to first-pass metabolism in the liver and the absolute bioavailability of isosorbide mononitrate from Ismo tablets is nearly 100%. The rate of clearance of Ismo is the same in healthy young adults, in patients with various degrees of renal, hepatic, or cardiac dysfunction, and in the elderly.

Several well-controlled studies have demonstrated that active nitrates were indistinguishable from placebo after 24 hours (or less) of continuous therapy due to the development of tolerance. Only after nitrates are absent from the body for several hours is their antianginal efficacy restored.

The drug-free interval sufficient to avoid tolerance to isosorbide mononitrate is not completely defined. The only regimen shown to avoid development of tolerance with isosorbide mononitrate involves two daily doses of Ismo tablets given 7 hours apart, so there is a gap of 17 hours between the second dose of each day and the first dose of the next day. Taking account of the relatively long half-life of isosorbide mononitrate this result is consistent with those obtained for other organic nitrates.

The same twice-daily regimen of Ismo tablets successfully avoided significant rebound/withdrawal effects. In studies of other nitrates, the incidence and magnitude of such phenomena appear to be highly dependent upon the schedule of nitrate administration.

Contraindications Allergic reactions are extremely rare, but do occur. Ismo is contraindicated in patients allergic to it.

Warnings Because the effects of Ismo are difficult to terminate rapidly and have not been established in patients with acute myocardial infarction (MI) or congestive heart failure (CHF), this drug is not recommended in these patients. If Ismo is used in these patients, careful clinical or hemodynamic monitoring is required to avoid the hazards of hypotension and tachycardia.

Precautions GENERAL Severe hypotension, particularly with upright posture, may occur with even small doses. Therefore, use with caution in patients who may be volume depleted or who are already hypotensive. Paradoxical bradycardia and increased angina pectoris may accompany Ismo-induced hypotension.

Nitrates may aggravate angina caused by hypertrophic cardiomyopathy.

INFORMATION FOR PATIENTS Tell patients they must carefully follow the prescribed dosing schedule (2 doses taken 7 hours apart) to maintain the antianginal effect (eg, take first dose on awakening and second dose 7 hours later).

Daily headaches sometimes accompany treatment with nitrates, including Ismo, and are a marker of drug activity. Patients with headaches should not alter their treatment schedule since loss of headache may be associated with simultaneous loss of antianginal efficacy. Headaches may be treated with aspirin and/or acetaminophen without affecting the antianginal activity of Ismo.

Light-headedness on standing, especially just after rising from a recumbent or seated position, may occur. This may be more frequent in patients who have consumed alcohol.

DRUG INTERACTIONS Vasodilating effects of Ismo may be additive with those of other vasodilators, especially alcohol.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY No carcinogenic effects were observed in mice or rats exposed to oral Ismo, nor were adverse effects on rat fertility observed.

No mutagenic activity was seen in *in vitro* or *in vivo* assays.

PREGNANCY CATEGORY C Ismo has been shown to have embryocidal effects in rats and rabbits at doses at least 70 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefit justifies potential fetal risk.

NURSING MOTHERS Excretion in human milk is unknown. Use caution if administered to a nursing woman. **PEDIATRIC USE** Safety and effectiveness have not been established.

Adverse Reactions Frequency of Adverse Reactions (Discontinuations)* Occurring in >1% of Subjects

	6 Controlled U.S. Studies		92 Clinical Studies
Dose	Placebo	20 mg	(varied)
Patients	204	219	3344
Headache	9% (0%)	38% (9%)	19% (4.3%)
Dizziness	1% (0%)	5% (1%)	3% (0.2%)
Nausea, Vomiting	<1% (0%)	4% (3%)	2% (0.2%)

*Some individuals discontinued for multiple reasons.

Fewer than 1% of patients reported each of the following (in many cases a causal relationship is uncertain): Cardiovascular: angina pectoris, arrhythmias, atrial fibrillation, hypotension, palpitations, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope. Dermatologic: pruritus, rash. Gastrointestinal: abdominal pain, diarrhea, dyspepsia, tenesmus, tooth disorder, vomiting. Genitourinary: dysuria, impotence, urinary frequency. Miscellaneous: asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors. Musculoskeletal: arthralgia. Neurologic: agitation, anxiety, confusion, dyscoordination, hypoesthesia, hypokinesia, increased appetite, insomnia, nervousness, nightmares. Respiratory: bronchitis, pneumonia, upper respiratory tract infection.

Rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeing patients (See **Overdosage**).

Overdosage The ill effects of overdosage are generally related to the ability of Ismo to induce vasodilation, venous pooling, reduced cardiac output and hypotension. Symptoms may include increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially with upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Serum levels have no role in managing overdosage. The likely lethal dose in humans is unknown.

There is neither a specific antidote to Ismo overdosage, nor data to suggest a means for accelerating its elimination from the body; dialysis is ineffective. Hypotension associated with Ismo overdosage results from venodilation and arterial hypovolemia; therefore, direct therapy toward an increase in central fluid volume. Use of arterial vasoconstrictors (eg, epinephrine) is likely to do more harm than good. In patients with renal disease or CHF, treatment of Ismo overdosage may be difficult and require invasive monitoring.

Methemoglobinemia has occurred in patients receiving other organic nitrates, and probably could occur as a side effect of Ismo. There are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Suspect the diagnosis in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO₂. Classically, methemoglobinemic blood is chocolate brown, without color change on exposure to air. The treatment of choice for methemoglobinemia is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION The recommended regimen of Ismo tablets is 20 mg (one tablet) twice daily, with the two doses given 7 hours apart. For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later. This dosing regimen provides a daily nitrate-free interval to avoid the development of refractory tolerance (see **Clinical Pharmacology**).

Well-controlled studies have shown that tolerance to Ismo tablets is avoided when using the twice daily regimen in which the two doses are given 7 hours apart. This regimen has been shown to have antianginal efficacy beginning 1 hour after the first dose and lasting at least 5 hours after the second dose. The duration (if any) of antianginal activity beyond 12 hours has not been studied; large controlled studies with other nitrates suggest that no dosing regimen should be expected to provide more than 12 hours of continuous antianginal efficacy per day.

Dosage adjustments are not necessary in the elderly patients or in patients with altered renal or hepatic function.

This Brief Summary is based upon the current Ismo direction circular, CI 4127-1, Issued January 10, 1992.

A-H-ROBINS

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FOR THE PREVENTION OF ANGINA PECTORIS*...

Ismo[®]

20 mg tablets

(isosorbide mononitrate)

ACTIVITY YOU CAN COUNT ON

- Demonstrated efficacy for at least 12 hours after the first dose (ie, 5 hours after the second dose)
- Avoids tolerance and rebound when dosed as recommended[†]

The most common side effect, headache, may be resolved with mild analgesics. As with other long-acting nitrates, Ismo is not recommended in patients with acute myocardial infarction or congestive heart failure.

*Ismo is not recommended for use in aborting acute anginal episodes.

†The dosing schedule of 20 mg, twice daily, 7 hours apart (with a 17-hour dose-free interval) must be followed carefully.

Please see brief summary of prescribing information on adjacent page.



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Counting Words: Two initials are considered one word, each abbreviation is considered one word, and figures consisting of a dollar sign and five numerals or less are considered one word. Cities and states consisting of two words or more are counted as one word. "New York" and "Salt Lake City" Zip code is considered one word and must appear in all ads. Telephone number with area code is considered one word. When box numbers are	CONNECTICUT — Otolaryngologist — BC-DE in joinbury, four member general otolaryngology group. Competitive salary and solid pension benefits. Modern 300 plus bed hospital. Growing community — great family area/schools. Direct inquiries and CV to: R-111111 1-800-477-7777	DEBILIN, OHIO — Multi-specialty group seeks BC-DE otolaryngologist to serve growing patient load. Northern Ohio college town serving drawing area of 275,000. Salary, liberal benefits first year with full shareholder status available thereafter. Send CV to: Dr. VanDyke, 224 West Lorain, Oberlin, OH 44074.

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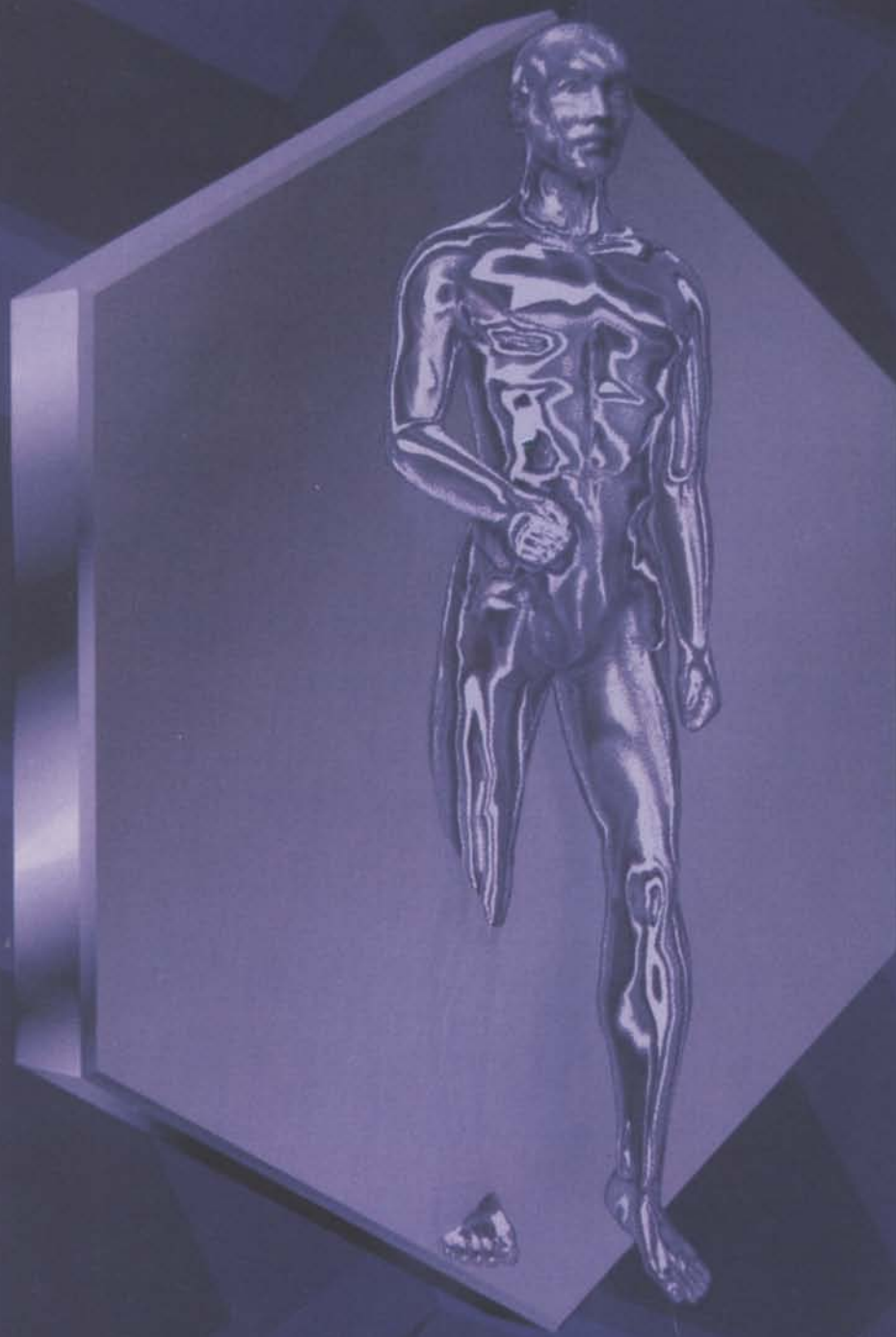
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Consistent clinical efficacy¹ at the end of treatment
in the mild to moderate adult infections
you see most often

95%

(N= 365) 62% cured
33% improved

Secondary bacterial infection of acute bronchitis

Due to *S. pneumoniae*, *H. influenzae* (including β -lactamase-producing strains), and
M. catarrhalis (including β -lactamase-producing strains).

93%

(N= 203) 54% cured
39% improved

Acute bacterial exacerbations of chronic bronchitis

Due to *S. pneumoniae*, *H. influenzae* (including β -lactamase-producing strains), and
M. catarrhalis (including β -lactamase-producing strains).

96%

(N= 83) 65% cured
31% improved

Pneumonia

Due to *S. pneumoniae* and *H. influenzae* (non- β -lactamase-producing strains only).

97%

(N= 192) 65% cured
32% improved

Acute maxillary sinusitis

Due to *S. pneumoniae*, *H. influenzae* (non- β -lactamase-producing strains only), and *M. catarrhalis* (including β -lactamase-producing strains). Note: In a patient population with significant numbers of β -lactamase-producing organisms, loracarbef's clinical cure and bacteriological eradication rates were somewhat less than those observed with a product containing a β -lactamase inhibitor. Lorabid's decreased potential for toxicity compared to products containing β -lactamase inhibitors along with the susceptibility patterns of the common microbes in a given geographic area should be taken into account when considering the use of an antimicrobial.

97%

(N= 180) 85% cured
12% improved

Pharyngitis/tonsillitis

Due to *S. pyogenes*. Note: The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin administered by the intramuscular route. Lorabid is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of Lorabid in the subsequent prevention of rheumatic fever are not available at present.

94%

(N= 68) 87% cured
7% improved

Uncomplicated pyelonephritis

Due to *E. coli*.

90%

(N= 201) 84% cured
6% improved

Uncomplicated urinary tract infections

Due to *E. coli* and *S. saprophyticus*. Note: In considering the use of Lorabid in the treatment of cystitis, Lorabid's lower bacterial eradication rates and lower potential for toxicity should be weighed against the increased eradication rates and increased potential for toxicity demonstrated by some other classes of approved agents.

93%

(N= 137) 67% cured
26% improved

Uncomplicated skin and skin structure infections

Due to *S. aureus* (including penicillinase-producing strains) and *S. pyogenes*.

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in a suspension

NEW CLASS LORABID™ LORACARBEF

A STEP
BEYOND...



Reference

1. Data on file, Lilly Research Laboratories.

Lorabid™ loracarbef 200-mg Pulvules*

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: Lorabid is a synthetic β -lactam antibiotic of the carbapenem class for oral administration. Lorabid is indicated in the following mild to moderate infections caused by susceptible strains of designated microorganisms.

Secondary Bacterial Infection of Acute Bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β -lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis* (including β -lactamase-producing strains).

Acute Bacterial Exacerbations of Chronic Bronchitis caused by *S. pneumoniae*, *H. influenzae* (including β -lactamase-producing strains), or *M. catarrhalis* (including β -lactamase-producing strains).

Pneumonia caused by *S. pneumoniae* or *H. influenzae* (non- β -lactamase-producing strains only).

Otitis Media* caused by *S. pneumoniae*, *H. influenzae* (including β -lactamase-producing strains), *M. catarrhalis* (including β -lactamase-producing strains), or *Streptococcus pyogenes*.

Acute Maxillary Sinusitis* caused by *S. pneumoniae*, *H. influenzae* (non- β -lactamase-producing strains only), or *M. catarrhalis* (including β -lactamase-producing strains).

*In a patient population with significant numbers of β -lactamase-producing organisms, loracarbef's clinical cure and bacteriological eradication rates were somewhat less than those observed with a product containing a β -lactamase inhibitor. Lorabid's decreased potential for toxicity compared to products containing β -lactamase inhibitors along with the susceptibility patterns of the common microbes in a given geographic area should be taken into account when considering the use of an antimicrobial (see Clinical Studies section).

Pharyngitis and Tonsillitis caused by *S. pyogenes*. (The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin administered by the intramuscular route. Lorabid is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of Lorabid in the subsequent prevention of rheumatic fever are not available at present.)

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *S. pyogenes*. Abscesses should be surgically drained as clinically indicated.

Uncomplicated Urinary Tract Infections (cystitis) caused by *Escherichia coli* or *Staphylococcus saprophyticus*.*

NOTE: In considering the use of Lorabid in the treatment of cystitis, Lorabid's lower bacterial eradication rates and lower potential for toxicity should be weighed against the increased eradication rates and increased potential for toxicity demonstrated by some other classes of approved agents (see Clinical Studies section).

Uncomplicated Pyelonephritis caused by *E. coli*.

*Although treatment of infections due to this organism in this organ system demonstrated a clinically acceptable overall outcome, efficacy was studied in fewer than 10 infections.

Contraindication: known allergy to loracarbef or cephalosporin-class antibiotics.

Warnings: Because cross-hypersensitivity can occur among β -lactams, Lorabid should be given cautiously to penicillin-sensitive patients and discontinued if an allergic reaction occurs.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and should be considered in differential diagnosis of antibiotic-associated diarrhea.

Precautions: Lorabid may be administered to patients with impaired renal function. Total daily dosage should be reduced in patients with known or suspected renal impairment; because of the possibility of high and/or prolonged plasma concentrations.

Loracarbef should be given cautiously to patients receiving diuretics concurrently.

Prolonged use may result in overgrowth of nonsusceptible organisms.

Loracarbef should be given cautiously to patients with a history of colitis. Renal excretion of β -lactams is inhibited by probenecid and resulted in about an 80% increase in the AUC for loracarbef.

Safety and effectiveness have not been determined in pregnancy, lactation, and infants under 6 months of age. Caution should be exercised in prescribing Lorabid for these patients.

In geriatric patients who received the usual recommended adult doses in clinical studies, efficacy and safety were comparable to results in nongeriatric adult patients.

Adverse Reactions: Most adverse reactions in clinical trials were mild and transient. Only 1.5% of patients discontinued because of drug-related reactions, the most common of which were diarrhea, abdominal pain, and skin rashes.

All Patients

The incidence of the following adverse events was less than 1%, except as otherwise noted:

Gastrointestinal: Diarrhea, 4.1%; nausea, 1.9%; vomiting, 1.4%; abdominal pain, 1.4%; and anorexia.

Hypersensitivity: Skin rashes (1.2%), urticaria, pruritus, and erythema multiforme.

Central Nervous System: Headache (2.9%), somnolence, nervousness, insomnia, and dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN and creatinine.

Cardiovascular System: Vasodilatation.

Genitourinary: Vaginitis (1.3%), vaginal moniliasis (1.1%).

Pediatric Patients

The incidences of several adverse events were significantly different in the pediatric population versus the adult population respectively as follows: Diarrhea (5.8% vs 3.6%); nausea (0.0% vs 2.5%); vomiting (3.3% vs 0.5%); anorexia (2.3% vs 0.3%); headache (0.9% vs 3.2%); somnolence (2.1% vs 0.4%); rhinitis (6.3% vs 1.6%); rash (2.9% vs 0.7%).

β -Lactam Antimicrobial Class Labeling:

Although not observed in Lorabid clinical trials, the following have been reported in patients treated with β -lactam antibiotics:

Adverse Reactions—Anaphylaxis, Stevens-Johnson syndrome, serum-sickness-like reactions, aplastic anemia, hemolytic anemia, hemorrhage, agranulocytosis, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, and hepatic dysfunction, including cholestasis, and seizures.

Altered Laboratory Tests—Increased prothrombin time, positive direct Coombs' test, elevated LDH, pancytopenia, and neutropenia.

Overdosage: Hemodialysis has been shown to be effective in hastening the elimination of loracarbef from plasma in patients with chronic renal failure.

Dosage and Administration: Lorabid is administered orally either at least 1 hour prior to eating or at least 2 hours after eating.

Population/Infection	Dosage (mg)	Duration (days)
Adults (≥ 13 years)		
Secondary Bacterial Infection of Acute Bronchitis	200-400 q 12h	7
Acute Bacterial Exacerbation of Chronic Bronchitis	400 q 12h	7
Pneumonia	400 q 12h	14
Pharyngitis/Tonsillitis	200 q 12h	10
Sinusitis	400 q 12h	10
(See Clinical Studies and Indications and Usage for further information.)		
Uncomplicated Skin and Skin Structure Infections	200 q 12h	7
Uncomplicated cystitis	200 q 24h	7
(See Clinical Studies and Indications and Usage for further information.)		
Uncomplicated pyelonephritis	400 q 12h	14
Infants and Children (6 mos to 2 yrs)		
Acute Otitis Media*	30 mg/kg/day q 12h (divided doses)	10
(See Clinical Studies and Indications and Usage for further information.)		
Pharyngitis/Tonsillitis	15 mg/kg/day q 12h (divided doses)	10
Impetigo	15 mg/kg/day q 12h (divided doses)	7

*Clinical studies of otitis media were conducted with the suspension formulation only. Therefore, the capsule should not be substituted for the suspension in the treatment of otitis media.

Clinical Studies:

Loracarbef (L) vs β -Lactamase Inhibitor (C) in Acute Otitis Media (US)

Efficacy: A study of acute otitis media performed in a population with a significant incidence of β -lactamase-producing organisms compared loracarbef with a β -lactamase inhibitor. Using very strict evaluability and microbiologic/clinical response criteria at the 10- to 16-day posttherapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (success rates) were obtained:

Pathogen	% Due to Pathogen (N = 204)	Success Rate
<i>S. pneumoniae</i>	42.6%	Equivalent to C
<i>H. influenzae</i>	30.4%	L 9% less than C
<i>M. catarrhalis</i>	20.6%	L 19% less than C
<i>S. pyogenes</i>	6.4%	Equivalent to C
Overall	100.0%	L 12% less than C

Safety: The incidences of the most common adverse events were clinically and statistically significantly higher in the control group versus the loracarbef group.

Event	Loracarbef	Control
Diarrhea	15%	26%
Rash*	8%	15%

*Primarily in the diaper area in young children.

Loracarbef (L) vs Amoxicillin (A) in Acute Otitis Media (Europe)

Efficacy: A study of acute otitis media performed in a population with a lower incidence of β -lactamase-producing organisms than that usually seen in US trials compared loracarbef to amoxicillin. Using very strict evaluability and microbiologic/clinical response criteria at the 10- to 16-day posttherapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (success rates) were obtained:

Pathogen	% Due to Pathogen (N = 291)	Success Rate
<i>S. pneumoniae</i>	51.5%	Equivalent to A
<i>H. influenzae</i>	29.2%	L 14% greater than A
<i>M. catarrhalis</i>	15.8%	L 31% greater than A
<i>S. pyogenes</i>	3.4%	Equivalent to A
Overall	100.0%	Equivalent to A

Loracarbef (L) vs Doxycycline (D) in Acute Maxillary Sinusitis (Europe)

Efficacy: A study of acute maxillary sinusitis performed in a population with a lower incidence of β -lactamase-producing organisms than that usually seen in US trials compared loracarbef with doxycycline. Using very strict evaluability (sinus-puncture) criteria and microbiologic/clinical response criteria at the 1- to 2-week posttherapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (success rates) were obtained:

Pathogen	% Due to Pathogen (N = 210)	Success Rate
<i>S. pneumoniae</i>	47.6%	Equivalent to D
<i>H. influenzae</i>	41.4%	Equivalent to D
<i>M. catarrhalis</i>	11.0%	Equivalent to D
Overall	100.0%	Equivalent to D

Loracarbef (L) vs Cefaclor (C) in Uncomplicated Cystitis Study (US)

Efficacy: A study of cystitis compared loracarbef with cefaclor. Using very strict evaluability criteria and microbiologic/clinical response criteria at the 5- to 9-day posttherapy follow-up, the following bacterial eradication rates were obtained:

Pathogen	% Due to Pathogen (N = 186)	Eradication Rate
<i>E. coli</i>	77.4%	L 4% greater than C (L = 80%)
Other major Enterobacteriaceae	12.5%	Equivalent to C (L = 61%)
<i>S. saprophyticus</i>	3.8%	Equivalent to C

Loracarbef (L) vs Quinolone (Q) in Uncomplicated Cystitis (Europe)

Efficacy: A study of cystitis compared loracarbef with an oral quinolone. Using very strict evaluability criteria and microbiologic/clinical response criteria at the 5- to 9-day posttherapy follow-up, the following bacterial eradication rates were obtained:

Pathogen	% Due to Pathogen (N = 189)	Eradication Rate
<i>E. coli</i>	82.0%	L 7% less than Q (L = 81%)
Other major Enterobacteriaceae	10.1%	L 32% less than Q (L = 50%)

PV 2731 AMP

[032592]

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.



Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00985
A Subsidiary of Eli Lilly and Company
Indianapolis, Indiana 46285

Lorabid™ (loracarbef)

Lorabid™ (loracarbef)

Lorabid™ (loracarbef)

THE SUPRAX DIFFERENCE

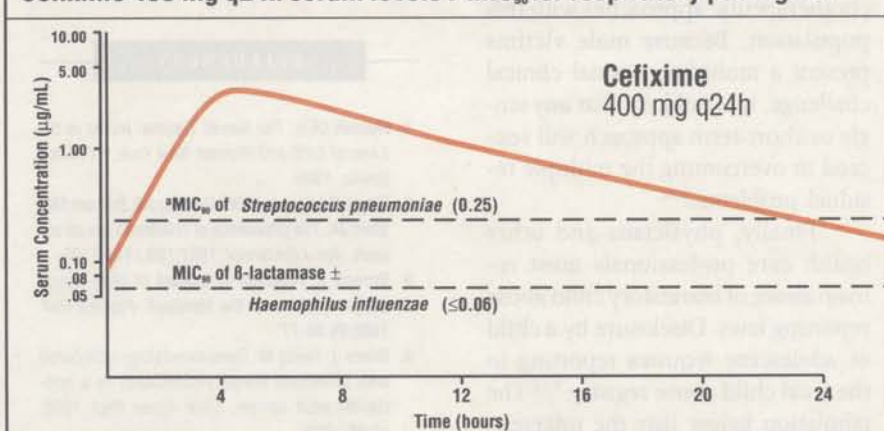


SUPRAX[®] Maintains Inhibitory Concentrations Above MIC₉₀ for Virtually 24 Hours*

For β -lactam antibiotics...
In order to achieve an optimal
antibacterial effect, antibiotic
concentrations must exceed
the MIC₉₀ for the majority of
the dosing interval.¹

*Although a useful guide, *in vitro*
activity does not necessarily
correlate with clinical response.

Cefixime 400 mg q24h serum levels v MIC₉₀ for respiratory pathogens^{2,3*}



*MIC₉₀ values from Jones and Barry.³

ONCE-A-DAY SUPRAX®

cefixime/Lederle

400 mg Tablets

24 HOUR POWER

References:

1. Ebert SC, Craig WA. Pharmacodynamic properties of antibiotics: application to drug monitoring and dosage regimen design. *Infect Control Hosp Epidemiol*. 1990;11(6):319-326.
2. Schentag JJ. Pharmacokinetic profiles as predictors of therapeutic success. In: *Respiratory Infections: Therapeutic Considerations in a Dynamic Environment*. Lederle Laboratories; 1990. Data on file. Lederle Laboratories, Pearl River, NY.
3. Jones RN, Barry AL. Antimicrobial activity, spectrum and recommendations for disk diffusion susceptibility testing of ceftibuten (7432-S; SCH 39720), a new orally administered cephalosporin. *Antimicrob Agents Chemother*. 1988;32(10):1576-1582.
4. Data on file. Lederle Laboratories, Pearl River, NY.

Brief Summary

SUPRAX® cefixime

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *S. pneumoniae* and *H. influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

Pharyngitis and Tonsillitis caused by *S. pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

*Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S. pneumoniae* was isolated from 47% of the patients, *H. influenzae* from 34%, *B. catarrhalis* from 15%, and *S. pyogenes* from 4%.

The overall response rate of *S. pneumoniae* to cefixime was approximately 10% lower and that of *H. influenzae* or *B. catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H. influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2- to 4-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at 2- to 4-Weeks Posttherapy
Based on Repeat Middle Ear Fluid Culture or Extrapolation From Clinical Outcome

Organism	Cefixime(a) 4 mg/kg bid	Cefixime(a) 8 mg/kg qd	Control(a) Drugs
<i>Streptococcus pneumoniae</i>	48/70 (69%)	18/22 (82%)	82/100 (82%)
<i>Haemophilus influenzae</i> beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
<i>Haemophilus influenzae</i> beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1(b)
<i>Moraxella (Branhamella)</i> <i>catarrhalis</i>	26/31 (84%)	5/5	18/24 (75%)
<i>Streptococcus pyogenes</i>	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive strains of *H. influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use.

SUPRAX® cefixime

Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuation, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION** in package insert.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferrocyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinistix® or Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Use in Pregnancy: Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (3.8%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness have been reported rarely.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia.

Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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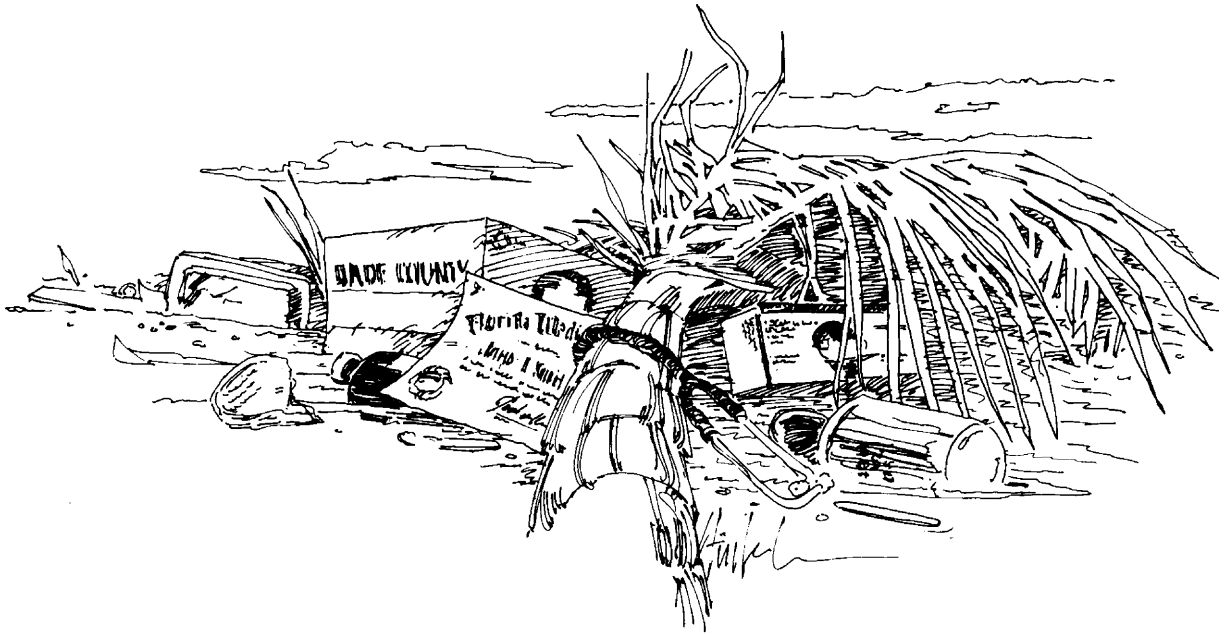
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Hurricane Andrew destroyed more than homes.

Andrew blew away the practices of nearly 1000 physicians.

Offices and equipment were flattened, patient and financial records were destroyed, and carefully nurtured careers were shattered ... all in a matter of hours. Now, the mammoth task of rebuilding southern Florida is underway.

Many of your Florida colleagues need help fast—their losses go far beyond what can be covered by insurance or government assistance. At the same time, their patients' need for skilled care is at a critical high.

The Florida Medical Foundation/Hurricane Relief Fund has been established to help the physicians who were hardest hit in the recent

disaster. Your tax-deductible contribution will directly benefit colleagues who are facing the challenge of a lifetime.

The American Medical Association joins the Florida Medical Association in appealing for your help. Send your contribution—or volunteer your services—but don't hesitate. Act now.

There is much to do, and no time to lose.

Send contributions payable to: *Florida Medical Foundation, Hurricane Relief Fund, PO Box 2411, Jacksonville, FL 32203. Or contact the Florida Medical Association, 904 356-1571.*

American Medical Association

Physicians dedicated to the health of America



NEW FOR ANGINA

THE ONE

CARDIZEM[®] CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules



ONCE A DAY

NEW FOR ANGINA

CARDIZEM[®] CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

PROVEN 24-HOUR CONTROL



ONCE A DAY

NEW FOR ANGINA

CARDIZEM[®] CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

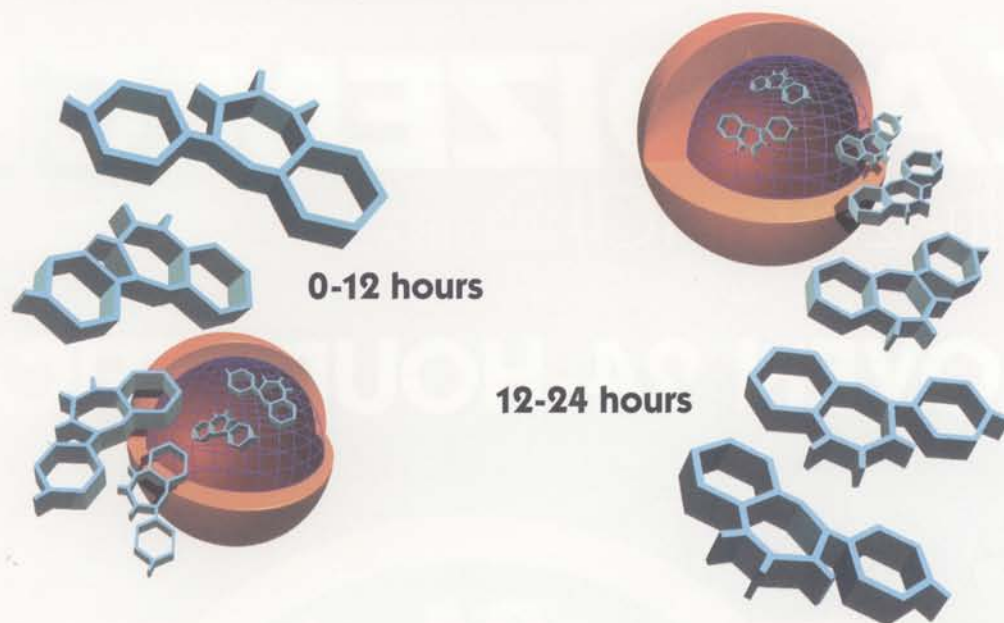
PROVEN 24-HOUR EFFICACY



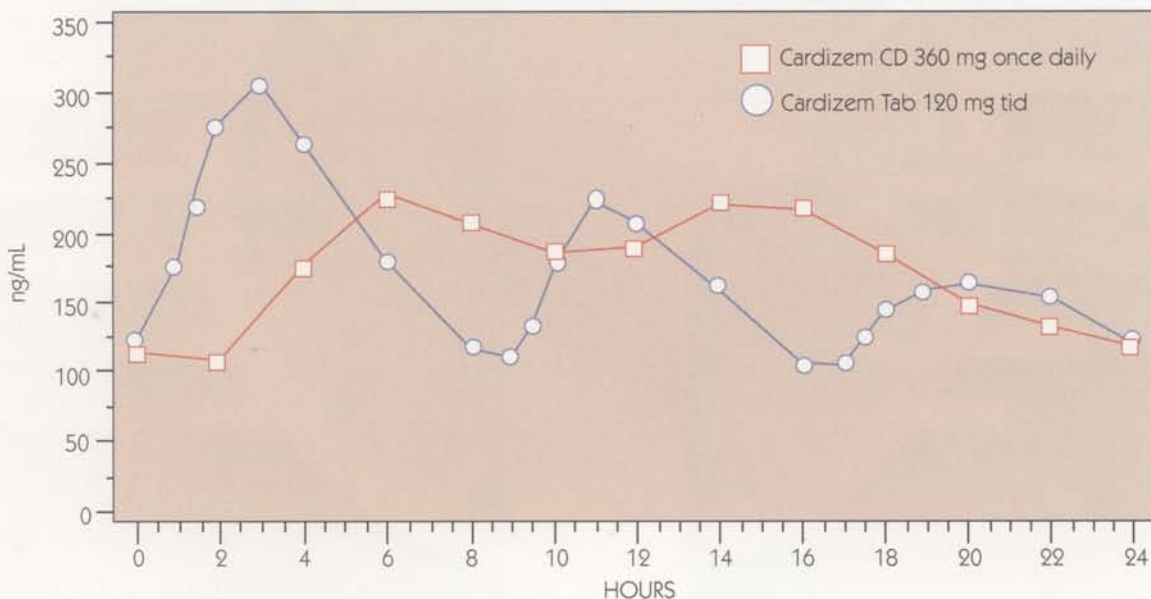
ONCE A DAY

IN ANGINA AND HYPERTENSION*

24-hour control through a **unique delivery system** designed specifically for diltiazem[†]



CARDIZEM CD provides 24-hour plasma levels similar to those of Cardizem tablets tid at steady state¹



One daily dose provides effective plasma levels¹

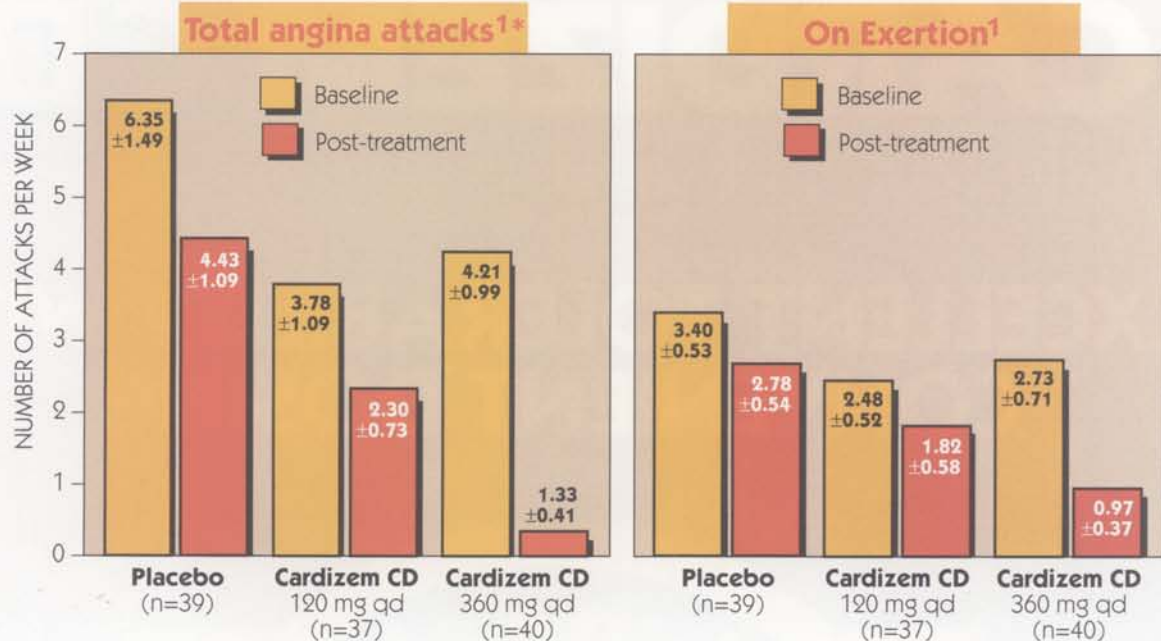
* Cardizem CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications. Cardizem CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

[†] Patent pending.

Please see brief summary of prescribing information on adjacent page.

IN ANGINA

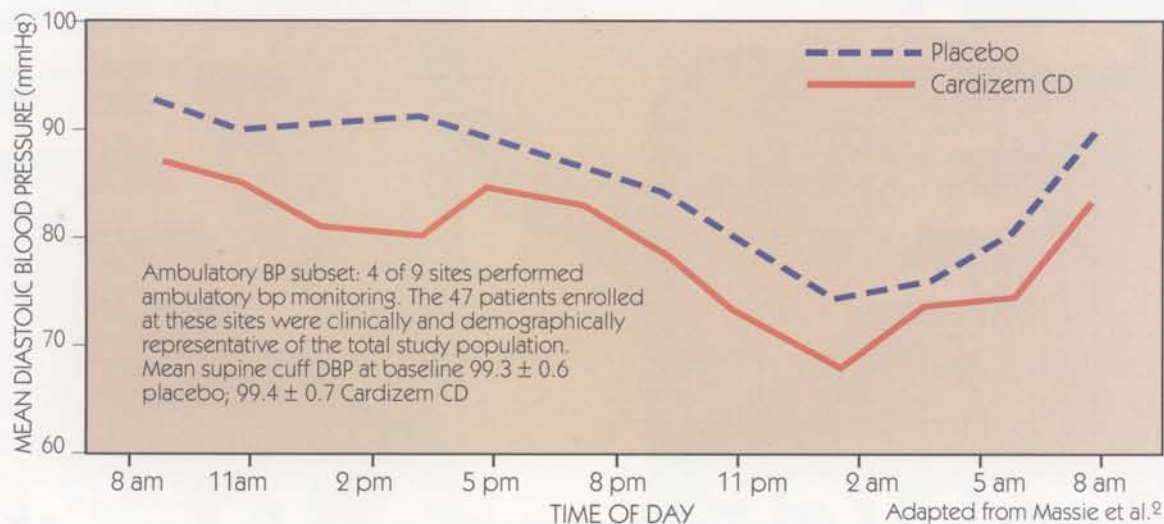
Reduces the frequency of angina attacks — **through 24 hours**¹



* At rest and on exertion.

IN HYPERTENSION

Consistent antihypertensive effect seen throughout 24 hours²



- Overall study results (127 patients) show a significant mean change at 24 hours in both diastolic ($P=0.0075$) and systolic ($P=0.0009$) blood pressure vs placebo²
- Cardizem CD average daily dose 268 mg/day

Unlike some once-a-day antihypertensives, titration to bid dosing is not necessary with Cardizem CD

Please see brief summary of prescribing information on adjacent page.

NEW FOR ANGINA

CARDIZEM[®] CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

**EXCELLENT TOLERABILITY WITH
CONVENIENT DOSING**



ONCE A DAY

IN ANGINA AND HYPERTENSION

Extremely well tolerated³

CARDIZEM CD Placebo-Controlled Angina and Hypertension Trials Combined		
Adverse Reaction	Cardizem CD n=607	Placebo n=301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of Cardizem CD capsules, Cardizem tablets, and Cardizem SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

COMPLIANCE-ENHANCING ONCE-DAILY DOSING



**120-mg
capsules**



**180-mg
capsules**



**240-mg
capsules**



**300-mg
capsules**

For angina or hypertensive patients, a recommended starting dose:

- **One 180-mg capsule daily**
- **If necessary, titrate to optimum response**

LOWER PRICE

Based on average wholesale prices using equivalent mg/day doses⁴:

- **35% lower cost than Cardizem® (diltiazem HCl) tablets for angina**
— Cardizem tablets are available as 30, 60, 90, and 120 mg
- **25% lower cost than Cardizem® SR (diltiazem HCl) capsules for hypertension**
— Cardizem SR capsules are available as 60, 90, and 120 mg

Please see brief summary of prescribing information on adjacent page.



ONCE-A-DAY CARDIZEM[®] CD (diltiazem HCl)

24-HOUR CONTROL OF ANGINA AND HYPERTENSION

Brief Summary of
Prescribing Information as of October 1992 (2)

CARDIZEM[®] CD (diltiazem HCl)

Capsules CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

- Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
- Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24%–6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
- Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
- Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General

CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (56%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Available as
Once-A-Day

120-mg capsules

180-mg capsules

240-mg capsules

300-mg capsules

Rx
Cardizem CD
Start with one
180-mg
capsule daily

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined		
Adverse Reaction	CARDIZEM CD N=607	Placebo N=301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3200 patients, the most common events (i.e., greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%). In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarthral pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported.

However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of October 1992 (2)

Marion Merrell Dow Inc.
Kansas City, MO 64114

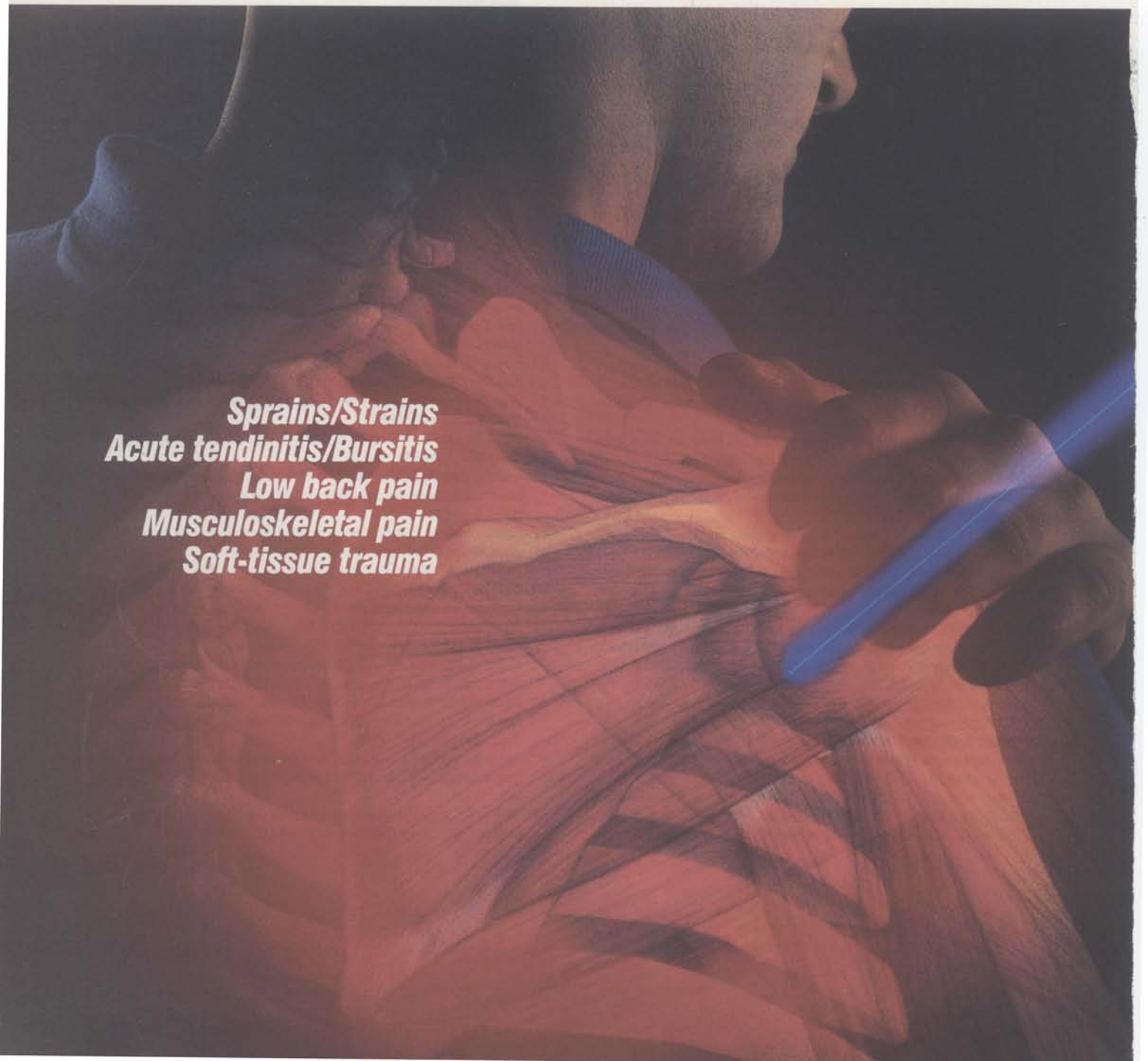
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References: 1. Data on file, Marion Merrell Dow Inc. 2. Massie BM, Der E, Herman TS, Topolski P, Park GD, Stewart WH. *Clin Cardiol.* 1992;15:365-368. 3. Cardizem CD prescribing information. 4. *Red Book Update.* 1992;11(10): 7.



MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO. 64114

Fast, effective relief for pain/inflammation.



***Sprains/Strains
Acute tendinitis/Bursitis
Low back pain
Musculoskeletal pain
Soft-tissue trauma***

Fast—pain relief may occur as fast as 20 minutes.

Effective—works at the pain site to provide relief for mild to moderate pain/inflammation.

Anti-inflammatory—nonsteroidal anti-inflammatory action helps patients return to normal activity.

Well tolerated—no narcotic-related side effects; no addiction potential.

As with other NSAIDs, the most frequent complaints are gastrointestinal. See Warnings, Precautions, and Adverse Reactions sections of prescribing information.

Convenient dosing—recommended starting dose is 550 mg, followed by 275 mg every 6 to 8 hours, as required. Total daily dose should not exceed 1375 mg.

Fast Relief. Fast Recovery.

550 MG TABLETS 275 MG TABLETS
Anaprox[®] DS Anaprox[®]
(NAPROXEN SODIUM)



For brief summary of prescribing information, please see next page.

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Brief Summary:

Contraindications: Patients who have had allergic reactions to NAPROSYN[®], ANAPROX[®] or ANAPROX[®] DS or in whom aspirin or other NSAIDs induce the syndrome of asthma, rhinitis, and nasal polyps. Because anaphylactic reactions usually occur in patients with a history of such reactions, question patients for asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy. If such symptoms occur, discontinue the drug.

Warnings: Serious GI toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation occur in about 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Inform patients of signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well and most spontaneous reports of fatal GI events are in this population. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Precautions: DO NOT GIVE NAPROSYN[®] (NAPROXEN) CONCOMITANTLY WITH ANAPROX[®] OR ANAPROX[®] DS (NAPROXEN SODIUM) SINCE THEY CIRCULATE IN PLASMA AS THE NAPROXEN ANION. Acute interstitial nephritis with hematuria, proteinuria, and nephrotic syndrome has been reported. Patients with impaired renal function, heart failure, liver dysfunction, patients taking diuretics, and the elderly are at greater risk of overt renal decompensation. If this occurs, discontinue the drug. Use with caution and monitor serum creatinine and/or creatinine clearance in patients with significantly impaired renal function. Use caution in patients with baseline creatinine clearance less than 20 mL/minute. Use the lowest effective dose in the elderly or in patients with chronic alcoholic liver disease or cirrhosis. Borderline elevations of liver tests may occur in up to 15% of patients. Elevations of SGPT or SGOT occurred in controlled trials in less than 1% of patients. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported rarely. If liver disease develops or if systemic manifestations occur (e.g., eosinophilia or rash), discontinue therapy. If steroid dosage is reduced or eliminated during therapy, do so slowly and observe patients closely for adverse effects, including adrenal insufficiency and exacerbation of arthritis symptoms. Determine hemoglobin values periodically for patients with initial values of 10 grams or less who receive long-term therapy. Peripheral edema has been reported. For patients with restricted sodium intake, note that each tablet contains approximately 25 or 50 mg (1 or 2 mEq) sodium. Use with caution in patients with fluid retention, hypertension or heart failure. The drug may reduce fever and inflammation, diminishing their diagnostic value. Conduct ophthalmic studies if any change or disturbance in vision occurs. **Information for Patients:** Side effects can cause discomfort and, rarely, more serious side effects, such as GI bleeding, may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with patients potential risks and benefits of NSAIDs, particularly when they are used for less serious conditions where treatment without NSAIDs may be acceptable. Patients should use caution for activities requiring alertness if they experience drowsiness, dizziness, vertigo or depression during therapy.

Laboratory Tests: Because serious GI tract ulceration and bleeding can occur without warning symptoms, follow chronically treated patients and inform them of the importance of the follow-up. **Drug Interactions:** Use caution when giving concomitantly with coumarin-type anticoagulants; a hydantoin, sulfonamide or sulfonylurea; furosemide; lithium; beta-blockers; probenecid; or methotrexate. **Drug/Laboratory Test Interactions:** May decrease platelet aggregation and prolong bleeding time or increase urinary values for 17-ketogenic steroids. Temporarily stop therapy for 72 hours before adrenal function tests. May interfere with urinary assays of SHIAA. **Carcinogenesis:** A 2-year rat study showed no evidence of carcinogenicity. **Pregnancy:** Category B. Do not use during pregnancy unless clearly needed. Avoid use during late pregnancy. **Nursing Mothers:** Avoid use. **Pediatric Use:** Single doses of 2.5-5 mg/kg (as naproxen suspension), with total daily dose not exceeding 15 mg/kg/day, are safe in children over 2 years of age.

Adverse Reactions: In a study, GI reactions were more frequent and severe in rheumatoid arthritis patients on 1650 mg/day naproxen sodium than in those on 825 mg/day. In children with juvenile arthritis, rash and prolonged bleeding times were more frequent, GI and CNS reactions about the same, and other reactions less frequent than in adults. Incidence Greater Than 1%, Probable Causal Relationship: GI: The most frequent complaints related to the GI tract: constipation, heartburn, abdominal pain, nausea, dyspepsia, diarrhea, stomatitis, CNS: headache, dizziness, drowsiness, light-headedness, vertigo. Dermatologic: itching (pruritus), skin eruptions, ecchymoses, sweating, purpura. Special Senses: tinnitus, hearing disturbances, visual disturbances. Cardiovascular: edema, dyspnea, palpitations. General: thirst. Incidence of reported reaction 3%-9%. Where unmarked, incidence less than 3%. Incidence Less Than 1%: Probable Causal Relationship: GI: abnormal liver function tests, colitis, GI bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting. Renal: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis. Hematologic: agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia. CNS: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness. Dermatologic: alopecia, photosensitive dermatitis, skin rashes. Special Senses: hearing impairment. Cardiovascular: congestive heart failure. Respiratory: eosinophilic pneumonitis. General: anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever). Causal Relationship Unknown: Hematologic: aplastic anemia, hemolytic anemia. CNS: aseptic meningitis, cognitive dysfunction. Dermatologic: epidermal necrolysis, erythema multiforme, photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa, Stevens-Johnson syndrome, urticaria. GI: non-peptic GI ulceration, ulcerative stomatitis. Cardiovascular: vasculitis. General: angioneurotic edema, hyperglycemia, hypoglycemia.

Overdosage: May have drowsiness, heartburn, indigestion, nausea, vomiting. A few patients have had seizures. Empty stomach and use usual supportive measures. In animals 0.5 g/kg of activated charcoal reduced plasma levels of naproxen.

Dosage and Administration for Mild to Moderate Pain, Dysmenorrhea and Acute Tendinitis and Bursitis: Recommended starting dose is 550 mg, followed by 275 mg every 6 to 8 hours. Total daily dose should not exceed 1375 mg.

Dosage and Administration for Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis: Recommended dose in adults is 275 mg or 550 mg twice daily. In patients who tolerate lower doses well, the dose may be increased to 1650 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. At this dosage, physicians should observe sufficient increased clinical benefits to offset potential increased risk.

Caution: Federal law prohibits dispensing without prescription. See package insert for full Prescribing Information.

#35

Revised 9/91

SYNTEX
SYNTEX PUERTO RICO, INC.
HUMACAO, P.R. 00966

Anaprox DS Anaprox
(NAPROXEN SODIUM)

What do these little suckers have to do with arthritis?

Plenty.

The little suckers are ticks.

More specifically, deer ticks.

They transmit Lyme disease, an infection that can cause recurring arthritis, and damage to the brain and heart.

Arthritis researchers, sponsored by the Arthritis Foundation, have been hard at work to find out why. Their findings have led to effective antibiotic treatments for Lyme disease.

The Arthritis Foundation sponsors hundreds of research projects as important as this one. We also provide continuing education for medical professionals, and practical help for people who have arthritis.

So support the Arthritis Foundation. Today. It's your contributions that make us tick.

YES, I'D LIKE TO HELP

Please activate my membership in the Arthritis Foundation, which helps support research and includes a year's subscription to *Arthritis Today*, the official magazine of the Foundation. Enclosed is my membership contribution of \$20 or more.

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P.O. Box 871706
Dallas, TX 75287-0277

☐ For instant membership, call toll-free 1-800-933-0032.
Mastercard and Visa accepted.



12499702

WHY CONSIDER TENORMIN BEFORE ALL OTHER BETA BLOCKERS?



- ▼ Convenient, once-daily dosing for all indications
- ▼ Effective control of blood pressure and angina
- ▼ Cardioprotection—improving survival during and after MI^{1,2*}
- ▼ Well-tolerated

I.V. INJECTION/TABLETS
TENORMIN[®]
(atenolol)

* Good clinical judgment suggests that patients who are dependent on sympathetic stimulation for adequate cardiac output and BP are not good candidates for beta blockade. In addition to patients excluded from the ISIS-1 study, those with borderline BP (ie, systolic < 120, especially if over age 60) are less likely to benefit.

References: 1. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet*. 1986;2:57-66. 2. Glanville DB, Lange RA, Hillis LD. Beneficial effect of long-term beta blockade after acute myocardial infarction in patients without anterograde flow in the infarct artery. *Am J Cardiol*. 1991;68:150-154.

See adjacent page for brief summary of prescribing information.

TENORMIN® (atenolol) 25, 50, 100 mg tablets

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

INDICATIONS AND USAGE: Hypertension. TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris. **Acute Myocardial Infarction:** TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (e.g., elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinitiated, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta₂-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenergic blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Additionally, caution should be used when TENORMIN I.V. injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and affects the heart can be reversed by administration of such agents as, dobutamine or isoproterenol with caution (see section on OVERDOSEAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients as a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering TENORMIN I.V. injection. Abrupt withdrawal of a beta-blocker might precipitate a thyroid storm. Therefore, if propranolol or isoproterenol is used to treat thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

Pregnancy and Fetal Injury: TENORMIN can cause fetal harm when administered to a pregnant woman. TENORMIN crosses the placental barrier and appears in cord blood. No studies have been performed on the use of TENORMIN in the first trimester and the possibility of fetal injury cannot be excluded. TENORMIN has been used under close supervision for the treatment of hypertension in the third trimester. Administration of TENORMIN for longer periods to pregnant women in the management of mild to moderate hypertension has been associated with intrauterine growth retardation. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Atenolol has been shown to produce a dose-related increase in embryofetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.*

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. TENORMIN may aggravate peripheral arterial circulatory disorders.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (SEE DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

Caution should be exercised with TENORMIN I.V. injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction. Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster), or Ames test (S typhimurium). Fertility of male and female rats evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg/kg/day (150 and 75 times the maximum recommended human antihypertensive dose*), respectively.

Use in Pregnancy: Pregnancy Category B. See WARNINGS - Pregnancy and Fetal Injury.

Nursing Mothers: Atenolol is excreted in milk at a ratio of 1:5 to 6:8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in children have not been established.

*Based on the maximum dose of 100 mg/day in 50 kg patient.

ADVERSE REACTIONS: Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

	Volunteered (US Studies)		Total - Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164)	Placebo (n = 206)	Atenolol (n = 399)	Placebo (n = 407)
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	3	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

TENORMIN® (atenolol) 25, 50, 100 mg tablets

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

	Conventional Therapy Plus Atenolol (n=244)	Conventional Therapy Alone (n=233)
Bradycardia	43 (18%)	24 (10%)
Hypotension	60 (25%)	34 (15%)
Bronchospasm	3 (1.2%)	2 (0.9%)
Heart Failure	46 (19%)	50 (24%)
Heart Block	11 (4.5%)	10 (4.3%)
BBB + Major		
Axis Deviation	16 (6.8%)	28 (12%)
Supraventricular Tachycardia	28 (11.5%)	45 (19%)
Atrial Fibrillation	12 (5%)	29 (11%)
Atrial Flutter	4 (1.6%)	7 (3%)
Ventricular Tachycardia	39 (16%)	52 (22%)
Cardiac Reinfection	0 (0%)	6 (2.6%)
Total Cardiac Arrests	4 (1.6%)	16 (6.9%)
Nonfatal Cardiac Arrests	4 (1.6%)	12 (5.1%)
Deaths	7 (2.9%)	16 (6.9%)
Cardiogenic Shock	1 (0.4%)	4 (1.7%)
Development of Ventricular Septal Defect	0 (0%)	2 (0.9%)
Regurgitation of Mitral	0 (0%)	2 (0.9%)
Renal Failure	1 (0.4%)	0 (0%)
Pulmonary Emboli	3 (1.2%)	0 (0%)

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to cataplexy; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash, Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (See DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSEAGE: Overdose with TENORMIN has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following TENORMIN overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdose of any beta-adrenergic blocking agent and which might also be expected in TENORMIN overdose are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENORMIN can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levaterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta₂ stimulant such as isoproterenol or terbutaline or oral aminophylline.

HYPOLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support. The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care unit or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN I.V. over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other adverse effects occur, TENORMIN should be discontinued.

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets

50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Elderly Patients or Patients with Renal Impairment: TENORMIN is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m². Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

The following maximum oral dosages are recommended for elderly, renally-impaired patients and for patients with renal impairment due to other causes:

	Creatinine Clearance (mL/min/1.73m ²)	Atenolol Elimination Half-Life (h)	Maximum Dosage
	15-35	16-27	50 mg daily
	<15	>27	25 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of TENORMIN: 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

TENORMIN Tablets: Tablets of 25 mg atenolol, NDC 0310-0107 (round, flat, uncoated white tablets with "T" debossed on one side and 107 debossed on the other side) are supplied in bottles of 100 tablets.

Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, banded) are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma. Store at controlled room temperature, 15°-30° C (59°-86° F). Dispense in well-closed, light resistant containers.

TENORMIN I.V. Injection

TENORMIN I.V. Injection, NDC 0310-0108, is supplied as 5 mg atenolol in 10 mL ampules of isotonic citrate-buffered aqueous solution. Protect from light. Keep ampules in outer packaging until time of use. Store at room temperature.

REV Y 03/92



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allergic rhinitis...

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for comfort^{1,2}

Once daily
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safety³⁻⁵



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Nasacort Nasal
Inhaler
(triamcinolone acetonide)

Turns patient complaints...Into patient compliance

Please see brief summary of prescribing information on adjacent page.

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Nasal
Inhaler

Turns patient complaints...Into patient compliance

ONCE DAILY
Nasacort[®]
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m²/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m²/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m²/day or 110 mcg/m²/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery.

Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m²/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m²/day and 7.0 mcg/m²/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m²/day in the rat and 320, 640 and 1280 mcg/m²/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m²/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see product circular for full prescribing information.

REFERENCES: 1. Winder J, Barker J, Bell T, et al: Intranasal triamcinolone acetonide aerosol versus beclomethasone dipropionate aqueous spray in perennial allergic rhinitis. *Medical Interface* 1992;5(6, suppl):16. 2. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Findlay S, Huber F, Garcia J, et al: Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. *Ann Allergy* 1992;68(3):228-232. 4. Storms W, Bronsky E, Findlay S, et al: Once daily triamcinolone acetonide nasal spray is effective for the treatment of perennial allergic rhinitis. *Ann Allergy* 1991;66(4):329-334. 5. Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992;89(6):1151-1156.

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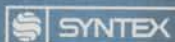
As with other NSAIDs, the most frequent
complaints are gastrointestinal.

Please see brief summary of prescribing information
on adjacent page.

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NAPROSYN[®]
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Also available in 375 and 250 mg tablets and in suspension 125 mg/5 mL



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NAPROSYN® (NAPROXEN) 500 mg tablets

Brief Summary:

Contraindications: Patients who have had allergic reactions to NAPROSYN, ANAPROX or ANAPROX DS or in whom aspirin or other NSAIDs induce the syndrome of asthma, rhinitis, and nasal polyps. Because anaphylactic reactions usually occur in patients with a history of such reactions, question patients for asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy. If such symptoms occur, discontinue the drug. **Warnings:** Serious GI toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** DO NOT GIVE NAPROSYN® (NAPROXEN) CONCOMITANTLY WITH ANAPROX® (NAPROXEN SODIUM) OR ANAPROX® DS (NAPROXEN SODIUM) SINCE THEY BOTH CIRCULATE IN PLASMA AS THE NAPROXEN ANION. Acute interstitial nephritis with hematuria, proteinuria, and nephrotic syndrome has been reported. Patients with impaired renal function, heart failure, liver dysfunction, patients taking diuretics, and the elderly are at greater risk of overt renal decompensation. If this occurs, discontinue the drug. Use with caution and monitor serum creatinine and/or creatinine clearance in patients with significantly impaired renal function. Use caution in patients with baseline creatinine clearance less than 20 mL/minute. Use the lowest effective dose in the elderly or in patients with chronic alcoholic liver disease or cirrhosis. With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. They may progress, remain unchanged, or be transient with continued therapy. Elevations of SGPT or SGOT occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported rarely. If liver disease develops or if systemic manifestations occur (e.g., eosinophilia or rash), discontinue therapy. If steroid dosage is reduced or eliminated during therapy, do so slowly and observe patients closely for adverse effects, including adrenal insufficiency and exacerbation of arthritis symptoms. Determine hemoglobin values periodically for patients with initial values of 10 grams or less who receive long-term therapy. Peripheral edema has been reported. Therefore, use with caution in patients with fluid retention, hypertension or heart failure. The drug's antipyretic and anti-inflammatory activities may reduce fever and inflammation, diminishing their diagnostic value. Conduct ophthalmic studies if any change or disturbance in vision occurs. For patients with restricted sodium intake, note that the suspension contains 8 mg/mL of sodium. **Information for Patients:** Side effects of NSAIDs can cause discomfort and, rarely, there are more serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with patients the potential risks and likely benefits of NSAID treatment, particularly when steroids are used for less serious conditions where treatment without NSAIDs may be an acceptable alternative. Patients should use caution for activities requiring alertness if they experience drowsiness, dizziness, vertigo or depression during therapy. **Laboratory Tests:** Because serious GI tract ulceration and bleeding can occur without warning symptoms, follow chronically treated patients for signs and symptoms of these and inform them of the importance of this follow-up. **Drug Interactions:** Use caution when giving concomitantly with coumarin-type anticoagulants; a hydantoin, sulfonamide or sulfonilurea; furosemide; lithium; beta-blockers; probenecid; or methotrexate. **Drug/Laboratory Test Interactions:** The drug may decrease platelet aggregation and prolong bleeding time or increase urinary values for 17-ketogenic steroids. Temporarily stop therapy for 72 hours before doing adrenal function tests. The drug may interfere with urinary assays of 5HIAA. **Carcinogenesis:** A 2-year rat study showed no evidence of carcinogenicity. **Pregnancy:** Category B. Do not use during pregnancy unless clearly needed. Avoid use during late pregnancy. **Nursing Mothers:** Avoid use in nursing mothers. **Pediatric Use:** Single doses of 2.5-5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are safe in children over 2 years of age. **Adverse Reactions:** In a study, GI reactions were more frequent and severe in rheumatoid arthritis patients on 1,500 mg/day than in those on 750 mg/day. In studies in children with juvenile arthritis, rash and prolonged bleeding times were more frequent, GI and CNS reactions about the same, and other reactions less frequent than in adults. **Incidence Greater Than 1%:** Probable Causal Relationship: GI: The most frequent complaints related to the GI tract: constipation; heartburn; abdominal pain; nausea; dyspepsia, diarrhea, stomatitis. CNS: headache; dizziness; drowsiness; light-headedness; vertigo. Dermatologic: itching (pruritus); skin eruptions; ecchymoses; sweating; purpura. Special Senses: tinnitus; hearing disturbances, visual disturbances. Cardiovascular: edema; dyspnea; palpitations. General: thirst. **Incidence Less Than 1%:** Probable Causal Relationship: GI: abnormal liver function tests, colitis, GI bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting. Renal: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis. Hematologic: agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia. CNS: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness. Dermatologic: alopecia, photosensitive dermatitis, skin rashes. Special Senses: hearing impairment. Cardiovascular: congestive heart failure. Respiratory: eosinophilic pneumonitis. General: anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever). Causal Relationship Unknown: Hematologic: aplastic anemia, hemolytic anemia. CNS: aseptic meningitis, cognitive dysfunction. Dermatologic: epidermal necrolysis, erythema multiforme, photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa, Stevens-Johnson syndrome, urticaria. GI: non-peptic GI ulceration, ulcerative stomatitis. Cardiovascular: vasculitis. General: angioneurotic edema, hyperglycemia, hypoglycemia. **Overdosage:** May have drowsiness, heartburn, indigestion, nausea, vomiting. A few patients have had seizures. Empty stomach and use usual supportive measures. In animals 0.5 g/kg of activated charcoal reduced plasma levels of naproxen. **Caution:** Federal law prohibits dispensing without prescription. See package insert for full Prescribing Information.

*Incidence of reported reaction 3%-9%.
Where unmarked, incidence less than 3%.



U.S. patent nos. 3,904,682, 3,998,966 and others.
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Encouragement

This message could be one of encouragement to you and, perhaps, certain of your patients.

Paget's disease of bone — not the rare disease it was once thought to be — is treatable in most cases. The earlier it is detected the more responsive to treatment it is likely to be. And detection can usually be accomplished with a few simple, non-invasive procedures.

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BRIEF SUMMARY

CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated in: (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second, or third degree AV block (22 of 10,119 patients, or 0.2%); 41% of these 22 patients were receiving concomitant β -adrenoceptor antagonists versus 17% of the total group. Concomitant use of diltiazem with β -blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single 60 mg dose of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction of $24\% \pm 6\%$) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with β -blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of serum transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with the histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Although Dilacor™ XR utilizes a slowly disintegrating matrix, caution should still be used in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of Dilacor™ XR.

Information for Patients. Dilacor™ XR capsules should be taken on an empty stomach. Patients should be cautioned that the Dilacor™ XR capsules should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with any agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using β -blockers or digitalis concomitantly with diltiazem hydrochloride (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers is usually well-tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of diltiazem hydrochloride with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium channel blockers should be titrated carefully.

References

1. Graney WF: Clinical experience with a once-daily, extended-release formulation of diltiazem in the treatment of hypertension. *Am J Med* 1992;93(Suppl 2A): 565-645.
2. 1992 Drug Topics® Red Book® Update. Oradell, NJ, Medical Economics Co. Inc.; December 1992.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and an 18-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in male or female rats at oral doses of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem hydrochloride in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem hydrochloride is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Dilacor™ XR. It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The most common adverse events (frequency $\geq 1\%$) in placebo-controlled, clinical hypertension studies with Dilacor™ XR using daily doses up to 540 mg are listed in the table below with placebo-treated patients included for comparison.

MOST COMMON ADVERSE EVENTS
IN DOUBLE-BLIND, PLACEBO-CONTROLLED HYPERTENSION TRIALS*

Adverse Events (COSTART Term)	Dilacor™ XR n=303 # pts (%)	Placebo n=87 # pts (%)
rhinitis	29 (9.6)	7 (8.0)
headache	27 (8.9)	12 (13.8)
pharyngitis	17 (5.6)	4 (4.6)
constipation	11 (3.6)	2 (2.3)
cough increase	9 (3.0)	2 (2.3)
flu syndrome	7 (2.3)	1 (1.1)
edema, peripheral	7 (2.3)	0 (0.0)
myalgia	7 (2.3)	0 (0.0)
diarrhea	6 (2.0)	0 (0.0)
vomiting	6 (2.0)	0 (0.0)
sinusitis	6 (2.0)	1 (1.1)
asthenia	5 (1.7)	0 (0.0)
pain, back	5 (1.7)	2 (2.3)
nausea	5 (1.7)	1 (1.1)
dyspepsia	4 (1.3)	0 (0.0)
vasodilatation	4 (1.3)	0 (0.0)
injury, accident	4 (1.3)	0 (0.0)
pain, abdominal	3 (1.0)	0 (0.0)
arthrosis	3 (1.0)	0 (0.0)
insomnia	3 (1.0)	0 (0.0)
dyspnea	3 (1.0)	0 (0.0)
rash	3 (1.0)	1 (1.1)
tinnitus	3 (1.0)	0 (0.0)

*Adverse events occurring in 1% or more of patients receiving Dilacor™ XR.

The following additional events (COSTART Terms), listed by body system, were reported infrequently in all subjects and hypertensive patients who received Dilacor™ XR (n=425): Cardiovascular: First-degree AV block, arrhythmia, postural hypotension, tachycardia, pallor, palpitations, phlebitis, ECG abnormality, ST elevation; Nervous System: Vertigo, hypertonia, paresthesia, dizziness, somnolence; Digestive System: Dry mouth, anorexia, tooth disorder, eructation; Skin and Appendages: Sweating, urticaria, skin hypertrophy (nevus); Respiratory System: Epistaxis, bronchitis, respiratory disorder; Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhea, vaginitis, prostate disease; Metabolic and Nutritional Disorders: Gout, edema; Musculoskeletal System: Arthralgia, bursitis, bone pain; Hemic and Lymphatic Systems: Lymphadenopathy; Body as a Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise; Special Senses: Amblyopia (blurred vision), ear pain.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem hydrochloride has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (dopamine or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g. dopamine or levaterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation as well as the judgment and experience of the treating physician.

Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluating cases of overdosage.

Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 10.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

Please see product circular for full prescribing information.

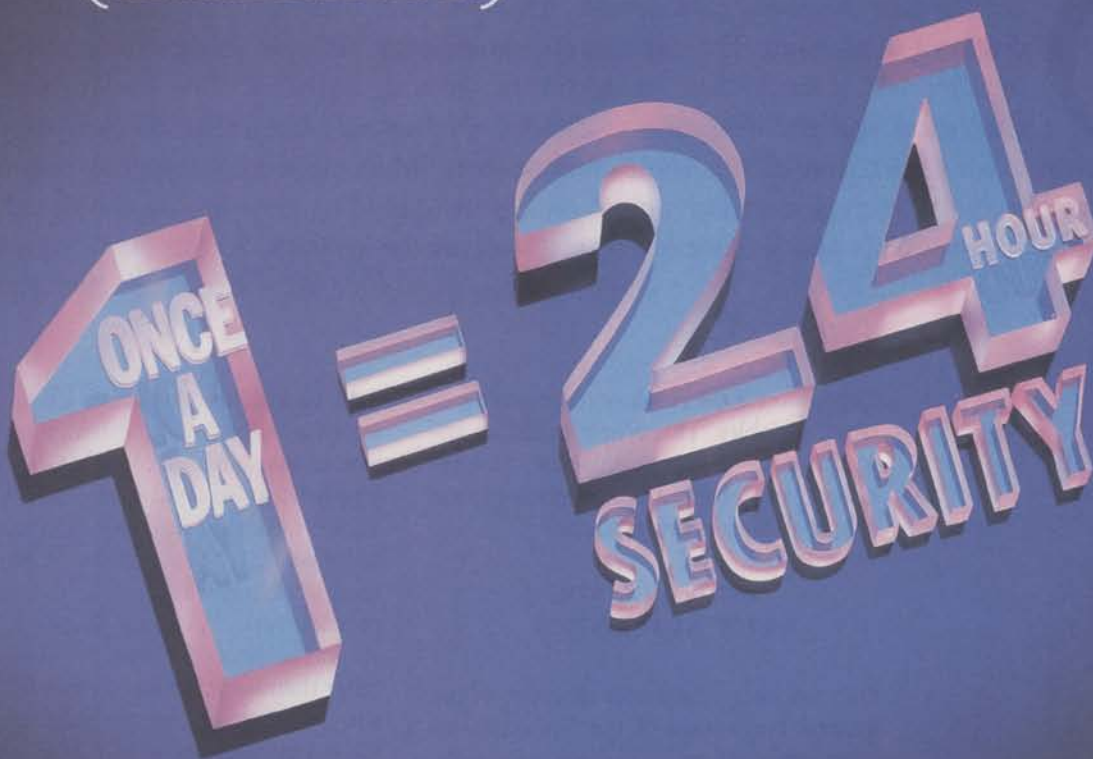
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NEW
120-mg strength
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Now, for hypertension
Once-a-day

DILACOR™ XR
(diltiazem HCl) EXTENDED
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DILACOR XR effectively lowers blood pressure
for 24 hours in the majority of patients¹

DILACOR XR offers the classic diltiazem safety
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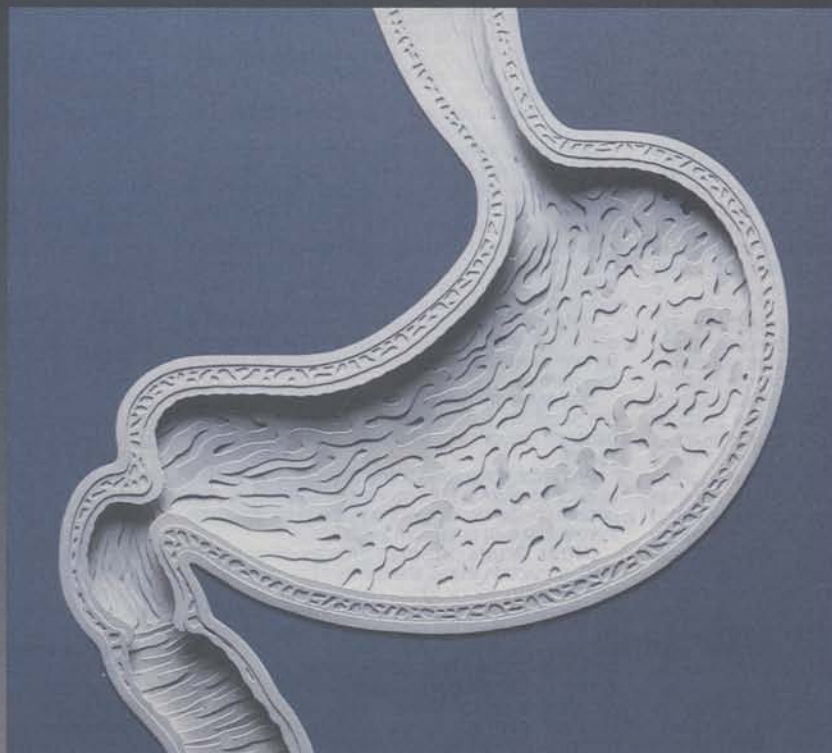
DILACOR XR makes diltiazem a cost-effective
choice for the treatment of hypertension²

Please see adjacent page for brief summary of prescribing information.

In arthritis therapy:

Because you're concerned about G.I. reactions...

NSAIDs may adversely affect the hematologic, hepatic, renal, and gastrointestinal systems, although G.I. reactions occur most frequently.



Start with

Voltaren[®] 25-50-75-MG TABLETS
diclofenac sodium

An established record of G.I. tolerability.*

*Contraindicated in patients hypersensitive to aspirin, other NSAIDs, or Voltaren. As with other NSAIDs, the most frequent complaints relate to the G.I. tract. In patients treated chronically with NSAID therapy, serious G.I. toxicity such as bleeding, ulceration, and perforation can occur. Elevations of SGOT and/or SGPT, some significant, have been reported in association with Voltaren treatment; cases of severe hepatic reactions have rarely been reported. Please see following page for brief summary of Prescribing Information.

Voltaren® diclofenac sodium

Enteric-Coated Tablets

Brief Summary (See full Prescribing Information)

INDICATIONS AND USAGE

Voltaren is indicated for acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

CONTRAINDICATIONS

Patients with hypersensitivity to it, in whom Voltaren, aspirin, or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions.

WARNINGS

Gastrointestinal Effects

Risk of G.I. ulcerations, bleeding and perforation with nonsteroidal anti-inflammatory therapy: Serious G.I. toxicity can occur at any time, with or without warning symptoms, during chronic treatment. The occurrence is about 1% after 3-6 months, 2-4% after a year. Patients should be informed of signs and symptoms of serious G.I. toxicity and what to do if it occurs. No subset of patients not at risk has been identified. Prior history of serious G.I. events and other risk factors of peptic ulcer disease, e.g., alcoholism, smoking, etc., have been associated with increased risk. The elderly and debilitated tolerate ulceration and bleeding less well than other individuals and most spontaneous reports of fatal G.I. events are in this population. G.I. ulceration and bleeding can occur without warning symptoms and chronically treated patients should be followed. It is recommended that patients be maintained on the lowest dose of diclofenac sodium possible consistent with achieving a satisfactory therapeutic response.

Hepatic Effects

As with other nonsteroidal anti-inflammatory drugs, elevations of one or more liver tests may occur during Voltaren therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations, (i.e., 1.2-3 times the upper limit of normal [ULN]), or greater elevations of transaminases occurred in about 15% of Voltaren-treated patients. The SGPT (ALT) test is probably the most sensitive indicator of liver injury. In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of SGOT (SGPT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during Voltaren treatment. In a large, open, controlled trial, meaningful elevations of SGOT and/or SGPT occurred in about 4% of 3700 patients treated for 2-6 months, including marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a lower incidence of borderline (1.2-3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of SGOT or SGPT was observed in patients randomized to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

Transaminase elevations were reversible on cessation of therapy, and among 51 patients in all studies with marked elevations, signs and symptoms of liver disease occurred in only 3 cases, and only 1 patient developed jaundice. Most patients with borderline elevations did not have therapy interrupted; transaminase elevations in most of these cases disappeared or did not progress. There were no identifying features to distinguish those patients who developed marked elevations from those who did not.

In addition to the enzyme elevations seen in clinical trials, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, have been reported.

Because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms, physicians should measure transaminases periodically in patients receiving long-term therapy with Voltaren. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label), which involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with Voltaren. Based on this experience the first transaminase measurement should be made no later than 8 weeks after the start of Voltaren treatment. As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Voltaren should be discontinued.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms), and the appropriate action to take should these signs and symptoms appear.

PRECAUTIONS

Allergic Reactions: As with other nonsteroidal anti-inflammatory drugs, allergic reactions including anaphylaxis, have been reported.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking Voltaren.

Renal Effects: Cases of significant renal failure in patients receiving Voltaren have been reported from postmarketing experience, but were not observed in over 4,000 patients in clinical trials during which serum creatinines and BUNs were followed serially. Since Voltaren metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be more closely monitored than subjects with normal renal function.

Porphyria: The use of diclofenac in patients with hepatic porphyria should be avoided.

Drug Interactions

Aspirin: Concomitant administration of Voltaren and aspirin is not recommended.

Anticoagulants: NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including Voltaren, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Voltaren, like other NSAIDs, through effects on renal prostaglandins, may cause increased toxicity of digoxin, methotrexate, and cyclosporine.

Lithium: Voltaren decreases lithium renal clearance and increases lithium plasma levels. In patients taking Voltaren and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Voltaren and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7-10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline, or digitoxin did not significantly affect the peak levels and AUC values of Voltaren.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: Voltaren increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Voltaren should be used during pregnancy only if the benefits to the mother justify the potential risk to the fetus. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of Voltaren during late pregnancy should be avoided.

Labor and Delivery

The effects of Voltaren on labor and delivery in pregnant women are unknown. However, as with other nonsteroidal anti-inflammatory drugs, it is possible that Voltaren may inhibit uterine contraction.

Nursing Mothers

Voltaren has been found in the milk of nursing mothers. As with other drugs that are excreted in milk, Voltaren is not recommended for use in nursing women.

Pediatric Use

Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3%, of patients. Peptic ulcer or G.I. bleeding occurred in clinical trials in less than 1% of approximately 1800 patients during their first 3 months of diclofenac treatment and in less than 2% of approximately 800 patients followed for 1 year. Comparative rates were 0.2% for peptic ulcer or G.I. bleeding in approximately 2000 diclofenac-treated patients and 0.6% in approximately 600 aspirin-treated patients.

In double-blind trials there were fewer minor gastrointestinal complaints in 1227 patients treated with Voltaren than in 721 patients treated with aspirin, 22% vs 33% (compared to 13% on placebo).

The following adverse reactions were reported in patients treated with Voltaren:

Incidence Greater Than 1% (All derived from clinical trials.)

Body as a Whole: Abdominal pain or cramps*, headache*, fluid retention, abdominal distention.

Digestive: Diarrhea*, indigestion*, nausea*, constipation*, flatulence, liver test abnormalities, PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special Senses: Tinnitus.

*Incidence, 3% to 9% (incidence of unmarked reactions is 1-3%)

Incidence Less Than 1% — Causal Relationship Probable (Adverse reactions reported only in worldwide postmarketing experience or in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Malaise, swelling of lips and tongue, photosensitivity, *anaphylaxis*, *anaphylactoid reactions*.

Cardiovascular: Hypertension, congestive heart failure.

Digestive: Vomiting, jaundice, melena, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *hemolytic anemia*, *aplastic anemia*, *agranulocytosis*, purpura, *allergic purpura*.

Metabolic and Nutritional Disorders: Azotemia.

Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability.

Respiratory: Epistaxis, asthma, laryngeal edema.

Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, *bullous eruption*, *erythema multiforme major*, angioedema, *Stevens-Johnson syndrome*.

Special Senses: Blurred vision, taste disorder, reversible hearing loss, scotoma.

Urogenital: Nephrotic syndrome, proteinuria, *oliguria*, *interstitial nephritis*, *capillary necrosis*, *acute renal failure*.

Incidence Less Than 1% — Causal Relationship Unknown (Adverse reactions reported only in worldwide postmarketing experience or in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Chest pain.

Cardiovascular: Palpitations, *flushing*, tachycardia, premature ventricular contractions, myocardial infarction.

Digestive: Esophageal lesions.

Hemic and Lymphatic: *bruising*.

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss*.

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination*, convulsions, *disorientation*, *psychotic reaction*.

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: Excess perspiration, *exfoliative dermatitis*.

Special Senses: Vitreous floaters, night blindness, amblyopia.

Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

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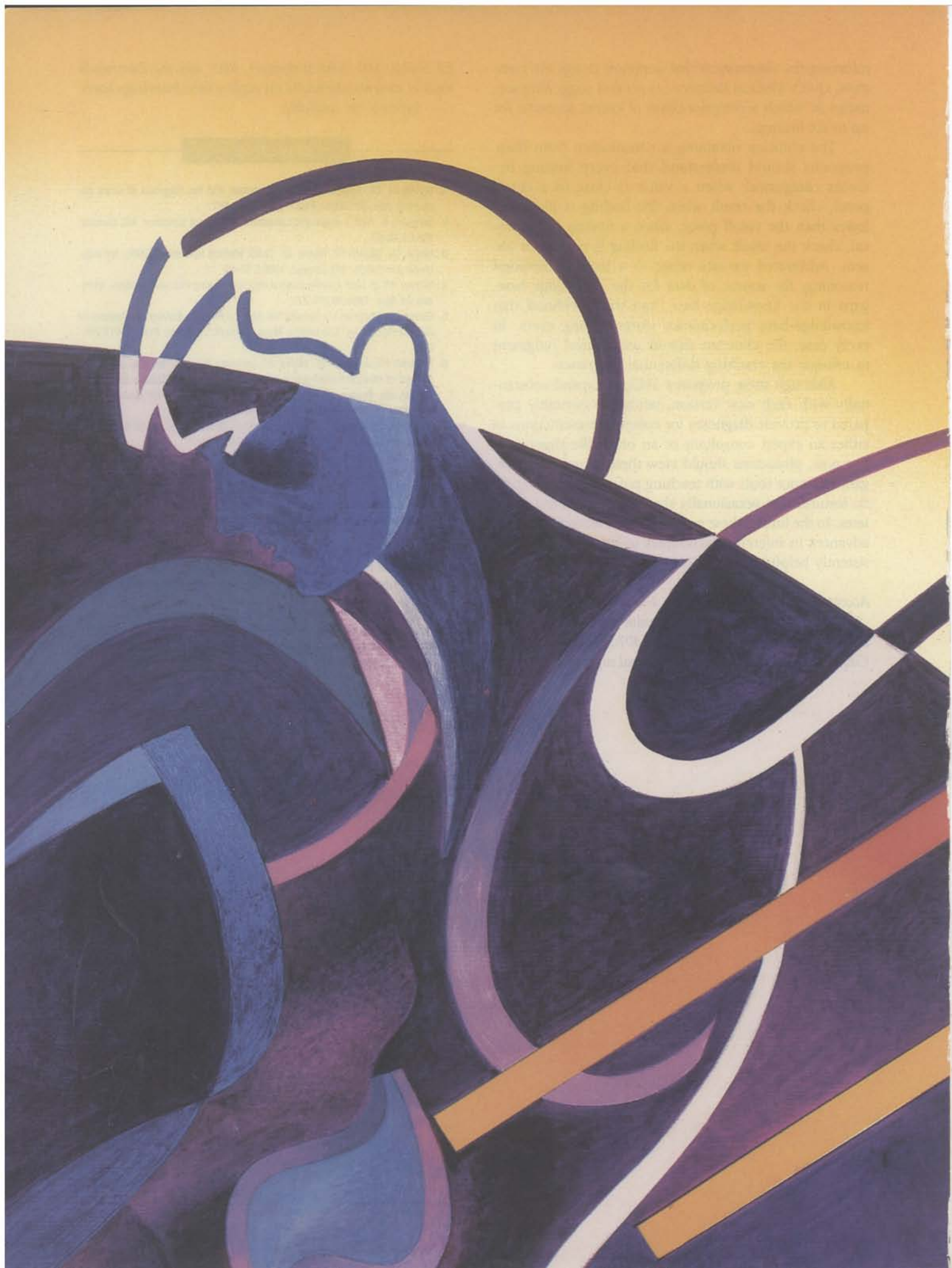
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RELAFEN[®]

NABUMETONE

**For the treatment of osteoarthritis
and rheumatoid arthritis**

- Efficacy comparable to naproxen or aspirin

A low incidence of peptic ulcers



Convenient once-a-day dosing

- Usual starting dose 1000 mg/day, taken
as two 500 mg tablets

Please see brief summary of prescribing information on adjacent page.



SmithKline Beecham
Pharmaceuticals

Philadelphia, PA 19101

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RELAFEN®
brand of nabumetone

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or PDR. The following is a brief summary.

CLINICAL PHARMACOLOGY: *Relafen* is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties in pharmacologic studies. As with other nonsteroidal anti-inflammatory agents, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect. The parent compound is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), a potent inhibitor of prostaglandin synthesis.

INDICATIONS AND USAGE: Acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS: Patients (1) who have previously exhibited hypersensitivity to it; (2) in whom *Relafen*, aspirin or other NSAIDs induce asthma, urticaria or other allergic-type reactions.

WARNINGS: Remain alert for ulceration and bleeding in patients treated chronically, even in the absence of previous G.I. tract symptoms.

In controlled clinical trials involving 1,677 patients treated with *Relafen* (1,140 followed for one year and 927 for two years), the cumulative incidence of peptic ulcers was 0.3% (95% CI: 0%, 0.6%) at three to six months, 0.5% (95% CI: 0.1%, 0.9%) at one year and 0.8% (95% CI: 0.3%, 1.3%) at two years. Inform patients of the signs and symptoms of serious G.I. toxicity and what steps to take if they occur. In patients with active peptic ulcer, weigh the benefits of *Relafen* therapy against possible hazards, institute an appropriate ulcer treatment regimen and monitor the patients' progress carefully.

In considering the use of relatively large doses (within the recommended dosage range), anticipate benefit sufficient to offset the potential increased risk of G.I. toxicity.

PRECAUTIONS: Because nabumetone undergoes extensive hepatic metabolism, no adjustment of *Relafen* dosage is generally necessary in patients with renal insufficiency. However, as with all NSAIDs, monitor patients with impaired renal function more closely than patients with normal renal function.

Evaluate patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of the development of a more severe hepatic reaction while on *Relafen* therapy. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue *Relafen*. Use *Relafen* cautiously in patients with severe hepatic impairment.

As with other NSAIDs, use *Relafen* cautiously in patients with a history of congestive heart failure, hypertension or other conditions predisposing to fluid retention.

Based on UV light photosensitivity testing, *Relafen* may be associated with more reactions to sun exposure than might be expected based on skin tanning types.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and the physician.

Exercise caution when administering *Relafen* with warfarin since interactions have been seen with other NSAIDs.

In two-year studies conducted in mice and rats, nabumetone had no statistically significant tumorigenic effect. Nabumetone did not show mutagenic potential in the Ames test and mouse micronucleus test *in vivo*. However, nabumetone- and 6MNA-treated lymphocytes in culture showed chromosomal aberrations at 80mcg/mL and higher concentrations (equal to the average human exposure to *Relafen* at the maximum recommended dose). Nabumetone did not impair fertility of male or female rats treated orally at doses of 320 mg/kg/day before mating. Pregnancy Category C: Nabumetone did not cause any teratogenic effect in rats given up to 400 mg/kg and in rabbits up to 300 mg/kg orally. However, increased post-implantation loss was observed in rats at 100 mg/kg orally and at higher doses (equal to the average human exposure to 6MNA at the maximum recommended human dose). There are no adequate, well-controlled studies in pregnant women. Use the drug during pregnancy only if clearly needed. Because of the known effect of prostaglandin-synthesis-inhibiting drugs on the human fetal cardiovascular system (closure of ductus arteriosus), use of *Relafen* during the third trimester of pregnancy is not recommended.

The effects of *Relafen* on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy.

It is not known whether nabumetone or its metabolites are excreted in human milk; however, 6MNA is excreted in the milk of lactating rats. Because of the possible adverse effects of prostaglandin-synthesis-inhibiting drugs on neonates, *Relafen* is not recommended for use in nursing mothers.

Safety and efficacy in children have not been established.

Of the 1,677 patients in U.S. clinical studies who were treated with *Relafen*, 411 patients (24%) were 65 years of age or older; 22 patients (1%) were 75 years of age or older. No overall differences in efficacy or safety were observed between these older patients and younger ones. Similar results were observed in a one-year, non-U.S. postmarketing surveillance study of 10,800 *Relafen* patients, of whom 4,577 patients (42%) were 65 years of age or older.

ADVERSE REACTIONS: Incidence $\geq 1\%$ —Probably Causally Related—Diarrhea (14%), dyspepsia (13%), abdominal pain (12%), constipation[†], flatulence[†], nausea[†], positive stool guaiac[†], dry mouth, gastritis, stomatitis, vomiting, dizziness[†], headache[†], fatigue, increased sweating, insomnia, nervousness, somnolence, pruritus[†], rash[†], tinnitus[†], edema[†].

[†]Incidence of reported reaction between 3% and 9%. Reactions occurring in 1% to 3% of the patients are unmarked.

Incidence $<1\%$ —Probably Causally Related[†]—Anorexia, cholestatic jaundice, duodenal ulcer, dysphagia, gastric ulcer, gastroenteritis, gastrointestinal bleeding, increased appetite, liver function abnormalities, melena, asthenia, agitation, anxiety, confusion, depression, malaise, paresthesia, tremor, vertigo, bullous eruptions, photosensitivity, urticaria, pseudoporphyria cutanea tarda, vasculitis, weight gain, dyspnea, hypersensitivity pneumonitis, albuminuria, azotemia, interstitial nephritis, abnormal vision, anaphylactoid reaction, angioneurotic edema.

Incidence $<1\%$ —Causal Relationship Unknown[†]—Bilirubinuria, duodenitis, eructation, gallstones, gingivitis, glossitis, pancreatitis, rectal bleeding, nightmares, acne, alopecia, erythema multiforme, Stevens-Johnson Syndrome, angina, arrhythmia, hypertension, myocardial infarction, palpitations, syncope, thrombophlebitis, asthma, cough, dysuria, hematuria, impotence, renal stones, taste disorder, fever, chills, anemia, leukopenia, granulocytopenia, thrombocytopenia, hyperglycemia, hypokalemia, weight loss.

[†]Adverse reactions reported only in worldwide postmarketing experience or in the literature are italicized.

OVERDOSAGE: If acute overdose occurs, empty the stomach by vomiting or lavage and institute general supportive measures as necessary. Activated charcoal, up to 60 grams, may effectively reduce nabumetone absorption. Coadministration of nabumetone with charcoal to man has resulted in an 80% decrease in maximum plasma concentrations of the active metabolite.

One overdose occurred in a 17-year-old female patient who had a history of abdominal pain and was hospitalized for increased abdominal pain following ingestion of 30 *Relafen* tablets (15 grams total). Stools were negative for occult blood and there was no fall in serum hemoglobin concentration. The patient had no other symptoms. She was given an H₂-receptor antagonist and discharged from the hospital without sequelae.

DOSAGE AND ADMINISTRATION: Recommended starting dose: 1000 mg taken as a single dose with or without food. Some patients may obtain more symptomatic relief from 1500 mg to 2000 mg daily. Dosages over 2000 mg daily have not been studied. Use the lowest effective dose for chronic treatment.

HOW SUPPLIED: Tablets: Oval-shaped, film-coated: 500 mg—white, imprinted with the product name RELAFEN and 500, in bottles of 100 and 500, and in Single Unit Packages of 100 (intended for institutional use only); 750 mg—beige, imprinted with the product name RELAFEN and 750, in bottles of 100 and 500, and in Single Unit Packages of 100 (intended for institutional use only).

Store at controlled room temperature (59° to 86°F) in well-closed container; dispense in light-resistant container.

500 mg 100's: NDC 0029-4851-20
500 mg 500's: NDC 0029-4851-25
500 mg SUP 100's: NDC 0029-4851-21

750 mg 100's: NDC 0029-4852-20
750 mg 500's: NDC 0029-4852-25
750 mg SUP 100's: NDC 0029-4852-21

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BRS-RL-L3

HELP PREVENT HEART ATTACK WITH A STROKE.



The back stroke. The crawl. The butterfly. It doesn't matter which you choose, as long as you do it up to 40 minutes, 3 to 4 times a week. Or try cycling or jogging. Any type of aerobic exercise program can help reduce your risk of heart attack and stroke. The only hard part is diving in. To learn more, contact the American Heart Association, 7272 Greenville Avenue, Box 47, Dallas, TX 75231-4596.

*You can help prevent heart disease and stroke.
We can tell you how.*

American Heart Association 

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From Mead Johnson Laboratories

Acute pain relief... from a nasal spray

A Potent Analgesic

- Synthetically derived opioid analgesic with sedative properties
- Efficacy comparable to IM meperidine at equipotent doses¹
- Somnolence (43%) is the most frequently reported side effect*

Effective in Acute Pain

- Demonstrated efficacy in relief of acute pain following invasive surgical procedures¹
- Also proven effective in the relief of acute migraine pain²
- Onset of pain relief within 15 minutes^{1,2}

In a Convenient Nasal Spray

- The only nasal spray analgesic
- Well suited for outpatient management of acute pain with appropriate medical instruction
- Not a federally controlled substance



STADOL[®] NS
(butorphanol tartrate) Nasal Spray

**Acute Pain Relief,
Delivered in Minutes**

*Across all clinical trials, including STADOL[®] Injectable and STADOL NS.¹ Patients should not perform potentially hazardous tasks (eg, driving, operating machinery). Alcohol should not be consumed while using STADOL NS.

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C-K62-6-92

1. Schwesinger WH, Reynolds JC, Harshaw DH, Frakes LA. Transnasal butorphanol and intramuscular meperidine in the treatment of postoperative pain. *Advances in Therapy*. 1992;9:123-129.

2. Diamond S, Freitag FG, Diamond ML, Urban G. Transnasal butorphanol in the treatment of migraine headache pain. *Headache Quarterly*. 1992;3:160-167.

3. STADOL[®] NS[®] package insert.

Please see brief summary of prescribing information on following page.

STADOL[®] NS[™]

(butorphanol tartrate) Nasal Spray

Acute Pain Relief, Delivered in Minutes



Brief Summary

INDICATIONS

STADOL[®] NS[™] (butorphanol tartrate) Nasal Spray is indicated for the management of pain when the use of an opioid analgesic is appropriate.

CONTRAINDICATIONS

STADOL NS is contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride.

WARNINGS

Patients Dependent on Narcotics

Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

PRECAUTIONS

Head Injury and Increased Intracranial Pressure

As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control

Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease

In patients with severe hepatic or renal disease the initial dosage interval for STADOL NS should be increased to 6-8 hours until the response has been well characterized. Subsequent doses should be determined by patient response rather than being scheduled at fixed intervals.

Cardiovascular Effects

Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Drug Interactions

Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (cimetidine, erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

The fraction of STADOL NS absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if STADOL NS is administered concomitantly with, or immediately following, a nasal vasoconstrictor.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Use in Ambulatory Patients

Drowsiness and dizziness related to the use of butorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc.). Patients should be told to use caution in such activities until their individual responses to butorphanol have been well characterized.

Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects.

Patients should be instructed on the proper use of STADOL NS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of butorphanol has not been adequately evaluated.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/sq.m.) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/sq.m.) subcutaneous dose.

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation.

Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. Pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/sq.m.) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (5.1 mg/sq.m.) and 60 mg/kg/oral (10.2 mg/sq.m.) also showed higher incidences of post implantation loss in rabbits.

Labor and Delivery

STADOL NS is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

Nursing Mothers

Butorphanol has been detected in milk following administration of STADOL Injectable to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 microgram/liter of milk in a mother receiving 2 mg IM four times a day).

Although there is no clinical experience with the use of STADOL NS in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

Pediatric Use

Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use

Initially a 1 mg dose of STADOL[®] NS[™] (butorphanol tartrate) Nasal Spray should generally be used in geriatric patients and 90-120 minutes should elapse before deciding whether a second 1 mg dose is needed.

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65. Elderly patients may be more sensitive to its side effects. Results from a long-term clinical safety trial suggest that elderly patients may be less tolerant of dizziness due to STADOL NS than younger patients.

ADVERSE REACTIONS

A total of 2446 patients were studied in butorphanol clinical trials. Approximately half received STADOL Injectable with the remainder receiving STADOL NS. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short- and long-term clinical trials in patients receiving butorphanol by any route and from post-marketing experience with STADOL Injectable. There has been no attempt to correct for placebo effect or to threshold the frequencies reported by placebo treated patients in controlled trials.

REACTIONS

The most frequently reported adverse experiences across all clinical trials with STADOL Injectable and STADOL NS were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with STADOL NS only, nasal congestion (13%) and insomnia (11%) were frequently reported.

The following adverse experiences were reported at a frequency of 1% or greater, and were considered to be probably related to the use of butorphanol:

BODY AS A WHOLE: asthenia/lethargy*, headache*, sensation of heat

CARDIOVASCULAR: VASODILATION*, PALPITATIONS

DIGESTIVE: ANOREXIA*, CONSTIPATION*, dry mouth*, nausea and/or vomiting (13%), stomach pain

NERVOUS: anxiety, confusion*, dizziness (19%), euphoria, floating feeling, INSOMNIA (11%), nervousness, paresthesia, somnolence (43%), TREMOR

RESPIRATORY: BRONCHITIS, COUGH, DYSPNEA*, EPISTAXIS*, NASAL CONGESTION (13%), NASAL IRRITATION*, PHARYNGITIS*, RHINITIS*, SINUS CONGESTION*, SINUSITIS, UPPER RESPIRATORY INFECTION*

SKIN AND APPENDAGES: sweating/clammy*, pruritus

SPECIAL SENSES: blurred vision, EAR PAIN, TINNITUS*, UNPLEASANT TASTE* (also seen in short-term trials with STADOL NS)

(Reactions occurring with a frequency of 3-9% are marked with an asterisk. * Reactions reported predominantly from long-term trials with STADOL NS are CAPITALIZED.)

The following adverse experiences were reported with a frequency of less than 1%, in clinical trials or from post-marketing experience and were considered to be probably related to the use of butorphanol.

CARDIOVASCULAR: hypotension

NERVOUS: abnormal dreams, agitation, drug dependence, dysphoria, hallucinations, hostility

SKIN AND APPENDAGES: rash/hives

UROGENITAL: impaired urination

(Reactions reported only from post-marketing experience are italicized.)

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term STADOL NS trials and from post-marketing experiences under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

BODY AS A WHOLE: edema

CARDIOVASCULAR: hypertension

NERVOUS: convulsion, delusions, depression

RESPIRATORY: apnea, shallow breathing

(Reactions reported only from post-marketing experience are italicized.)

DRUG ABUSE AND DEPENDENCE

Although the mixed agonist-antagonist opioid analgesics, as a class, have lower abuse potential than morphine, all such drugs can be and have been reported to be abused.

Chronic use of STADOL Injectable has been reported to result in mild withdrawal syndromes, and reports of overuse and self-reported addiction have been received.

Among 161 patients who used STADOL NS for 2 months or longer approximately 3% had behavioral symptoms suggestive of possible abuse. Approximately 1% of these patients reported significant overuse. Symptoms such as anxiety, agitation, and diarrhea were observed. Symptoms suggestive of opioid withdrawal occurred in 2 patients who stopped the drug abruptly after using 16 mg a day or more for longer than 3 months.

Special care should be exercised in administering butorphanol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is necessary, such patients should be closely supervised.

OVERDOSAGE

Clinical Manifestations

The clinical manifestations of overdose are those of opioid drugs, the most serious of which are hypoventilation, cardiovascular insufficiency and/or coma.

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment

The management of suspected butorphanol overdose includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

DOSEAGE AND ADMINISTRATION

Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, patients with hepatic or renal disease or in labor requires extra caution (see PRECAUTIONS). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

The usual recommended dose for initial nasal administration is 1 mg (1 spray in one nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60-90 minutes, an additional 1 mg dose may be given.

The initial two dose sequence outlined above may be repeated in 3-4 hours as needed.

Depending on the severity of the pain, an initial dose of 2 mg (1 spray in each nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients single additional 2 mg doses should not be given for 3-4 hours.

Safety and Handling

STADOL NS is an open delivery system with increased risk of exposure to health care workers.

In the priming process, a certain amount of butorphanol may be aerosolized, therefore the pump sprayer should be aimed away from the patient or other people or animals.

The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED

STADOL NS is supplied in a child-resistant prescription vial containing a metered-dose spray pump and protective clip with dust cover, a bottle of nasal spray solution, and a patient instruction leaflet. On average, one bottle will deliver 14-15 doses if no repriming is necessary.

NDC 0087-5650-41: 10 mg per mL, 2.5-mL bottle.

Storage Conditions

Store below 86°F (30°C). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CAUTION: Federal law prohibits dispensing without prescription.

Mead Johnson
LABORATORIES
A Bristol-Myers Squibb Company
Princeton, New Jersey 08543
U.S.A.

Introducing
FLOXIN[®] I.V.
(ofloxacin injection)
FOR INTRAVENOUS INFUSION

**EXTENSIVE
EXCELLENT**

- X** Coverage of both common and atypical organisms
- X** Highly effective* for hospitalized patients with:
Lower respiratory tract infections,[†] urinary tract infections,[†] and uncomplicated skin and skin structure infections[†]
- X** FLOXIN provides effective I.V. to oral sequential therapy with no change in dosage, potency, or coverage

NOTE: IN THE ABSENCE OF VOMITING OR OTHER FACTORS INTERFERING WITH THE ABSORPTION OF ORALLY ADMINISTERED DRUG, PATIENTS RECEIVE ESSENTIALLY THE SAME SYSTEMIC ANTIMICROBIAL THERAPY AFTER EQUIVALENT DOSES OF OFLOXACIN ADMINISTERED BY EITHER THE ORAL OR THE INTRAVENOUS ROUTE. THEREFORE, THE INTRAVENOUS FORMULATION DOES NOT PROVIDE A HIGHER DEGREE OF EFFICACY OR MORE POTENT ANTIMICROBIAL ACTIVITY THAN AN EQUIVALENT DOSE OF THE ORAL FORMULATION OF OFLOXACIN.

FLOXIN I.V. is indicated for the treatment of adults with mild to moderate infections caused by susceptible strains of the designated microorganisms in the infections listed above—when intravenous administration offers a route of administration advantageous to the patient (ie, patient cannot tolerate an oral dosage form, etc).

The safety and effectiveness of the intravenous formulation in treating patients with severe infections have not been established.

COVERAGE RESULTS



FLOXIN[®].i.v.
(ofloxacin injection)

A force to fight infection

The safety and efficacy of FLOXIN in children, adolescents (under 18), pregnant women, and lactating women have not been established. FLOXIN is contraindicated in persons with a history of hypersensitivity to FLOXIN or the quinolone group of antibacterial agents. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving therapy with quinolones, including ofloxacin. (See Warnings.) For information on additional adverse reactions that may occur, regardless of drug relationship, please see brief summary of Prescribing Information.

* FLOXIN tablets; patients receive essentially the same systemic antimicrobial therapy after equivalent doses of ofloxacin administered by either the oral or the intravenous route.
† Due to susceptible strains of indicated pathogens.

Please see brief summary of Prescribing Information on last page of this advertisement.

FLOXIN[®] I.V.

(ofloxacin injection)
FOR INTRAVENOUS INFUSION

400 mg
10 mL and
20 mL vials
100 mL
flexible
containers

FLOXIN[®] tablets

(ofloxacin tablets)

200 mg
300 mg
400 mg

Brief Summary

The following is a brief summary only. Before prescribing, see complete Prescribing Information in FLOXIN labeling.

CONTRAINDICATIONS: Ofloxacin is contraindicated in persons with a history of hypersensitivity to ofloxacin or members of the quinolone group of antimicrobial agents.

WARNINGS: THE SAFETY AND EFFICACY OF OFLOXACIN IN CHILDREN, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE PEDIATRIC USE, USE IN PREGNANCY, AND NURSING MOTHERS SUBSECTIONS IN THE PRECAUTIONS SECTION.)

In the immature rat, the oral administration of ofloxacin at 5 to 16 times the recommended maximum human dose based on mg/kg or 1 to 3 times based on mg/m² increased the incidence and severity of osteochondrosis. The lesions did not regress after 13 weeks of drug withdrawal. Other quinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY** in full Prescribing Information.)

Ofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ofloxacin should have a follow-up serologic test for syphilis after 3 months.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving therapy with quinolones, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, angioedema (including laryngeal, pharyngeal, or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to ofloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Severe hypersensitivity reactions (generally following multiple doses) characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with a fatal outcome have also been reported extremely rarely in patients receiving another quinolone. Similar reactions may occur with ofloxacin. The drug should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. (See **PRECAUTIONS AND ADVERSE REACTIONS**.) Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ofloxacin. Quinolones may also cause central nervous system stimulation, which may lead to tremors, restlessness, lightheadedness, confusion, and hallucinations. If these reactions occur in patients receiving ofloxacin, the drug should be discontinued and appropriate measures instituted. No evidence of an effect of ofloxacin on the electrical activity of the brain has been demonstrated. Ofloxacin does not alter the metabolism of glucose in the central nervous system based on positron emission tomography. It does not have effects upon the electrical patterns of brain function based on EEGs. However, until more information becomes available, ofloxacin, like all other quinolones, should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors (eg, concomitant drug therapy) that predispose to seizures. (See **PRECAUTIONS AND ADVERSE REACTIONS**.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an oral antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS**.)

PRECAUTIONS

General

Because a rapid or bolus intravenous injection may result in hypotension, OFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES. (See **DOSE AND ADMINISTRATION** in full Prescribing Information.)

Adequate hydration of patients receiving ofloxacin should be maintained to prevent the formation of highly concentrated urine.

In patients with impaired renal function (creatinine clearance ≤ 50 mL/min), alteration of the dosage regimen is necessary. (See **DOSE AND ADMINISTRATION** in full Prescribing Information.)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving some drugs in this class. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Information for Patients

Patients should be advised:

- to drink fluids liberally if able to take fluids by the oral route.
- that ofloxacin can cause dizziness and lightheadedness and that patients should know how they react to ofloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination. (See **WARNINGS AND ADVERSE REACTIONS**.)
- that ofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives, rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema, or other symptom of an allergic reaction. (See **WARNINGS AND ADVERSE REACTIONS**.)
- to avoid excessive sunlight or artificial ultraviolet light while receiving ofloxacin and to discontinue therapy if phototoxicity occurs.
- that if therapy with oral ofloxacin is initiated, then (1) mineral supplements, vitamins with iron or minerals, calcium, aluminum-, or magnesium-based antacids, or sucralfate should not be taken within the 2-hour period before or within the 2-hour period after taking oral ofloxacin (see **Drug Interactions**); and (2) oral ofloxacin should not be taken with food.

Drug Interactions

Antacids, Sucralfate, Metal Cations, Multivitamins

FLOXIN I.V.: There are no data concerning an interaction of intravenous quinolones with oral antacids, sucralfate, multivitamins, or metal cations. However, no quinolone should be coadministered with any solution containing multivalent cations (eg, magnesium) through the same intravenous line. (See **DOSE AND ADMINISTRATION** in full Prescribing Information.)

FLOXIN tablets: Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing calcium, magnesium, or aluminum, with sucralfate, with divalent or trivalent cations such as iron, or with multivitamins containing zinc may substantially interfere with the absorption of quinolones, resulting in systemic levels considerably lower than desired. These agents should not be taken within the 2-hour period before or within the 2-hour period after ofloxacin administration. (See **DOSE AND ADMINISTRATION** in full Prescribing Information.)

Caffeine: Interactions between ofloxacin and caffeine have not been detected.

Cimetidine: Cimetidine has demonstrated interference with the elimination of some quinolones. This interference has resulted in significant increases in half-life and AUC of some quinolones. The potential for interaction between ofloxacin and cimetidine has not been studied.

Cyclosporine: Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with some other quinolones. The potential for interaction between ofloxacin and cyclosporine has not been studied.

Nonsteroidal anti-inflammatory drugs: Concomitant administration of the nonsteroidal anti-inflammatory drug fenbufen with some quinolones, including ofloxacin, has been reported to increase the risk of CNS stimulation and convulsive seizures. Fenbufen is presently not an approved drug in the United States.

Probenecid: The concomitant use of probenecid with certain other quinolones has been reported to affect renal tubular secretion. The effect of probenecid on the elimination of ofloxacin has not been studied.

Theophylline: Although concurrent administration of some quinolones with theophylline may result in impaired elimination of theophylline, the extent of such impairment varies among different quinolones. Steady-state theophylline levels may increase when ofloxacin and theophylline are administered concurrently. In a pharmacokinetic study involving 15 healthy male subjects, steady-state peak theophylline concentration increased by an average of approximately 9%, and the AUC increased by an average of approximately 13% when oral ofloxacin and theophylline were administered concurrently. In clinical trials with intravenous ofloxacin, theophylline concentra-

tions were determined in 41 patients who were treated with both drugs. In 38 patients, no apparent elevation in the serum theophylline was discernible. Marginal increases above the theophylline therapeutic range were reported in 3 patients; clinical toxicity was, however, not reported in these 3 patients. Generally, patients receiving theophylline in clinical trials of the intravenous formulation of ofloxacin reported nausea more frequently than those patients not receiving theophylline. As with some other quinolones, concomitant administration of ofloxacin may prolong the half-life of theophylline, elevate serum theophylline levels, and may increase the risk of theophylline related adverse reactions. Theophylline levels should be closely monitored and theophylline dosage adjustments made, if appropriate, when ofloxacin is coadministered.

Warfarin: Some quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. Therefore, if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives, the prothrombin time or other suitable coagulation test should be closely monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted.

Ofloxacin was not mutagenic in the Ames bacterial test, *in vitro* and *in vivo* cytogenetic assay, sister chromatid exchange (Chinese hamster and human cell lines), unscheduled DNA repair (UDS) using human fibroblasts, dominant lethal assays, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocytes and mouse lymphoma assay.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Ofloxacin has not been shown to have any teratogenic effects at oral doses as high as 810 mg/kg/day (11 times the recommended maximum human dose based on mg/m² or 50 times based on mg/kg) and 160 mg/kg/day (4 times the recommended maximum human dose based on mg/m² or 10 times based on mg/kg) when administered to pregnant rats and rabbits, respectively. Additional studies in rats with oral doses up to 360 mg/kg/day (5 times the recommended maximum human dose based on mg/m² or 23 times based on mg/kg) demonstrated no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. Doses equivalent to 50 and 10 times the recommended maximum human dose of ofloxacin (based on mg/kg) were fetotoxic (ie, decreased fetal body weight and increased fetal mortality) in rats and rabbits, respectively. Minor skeletal variations were reported in rats receiving doses of 810 mg/kg/day, which is more than 10 times higher than the recommended maximum human dose based on mg/m².

There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers: In lactating females, a single oral 200-mg dose of ofloxacin resulted in concentrations of ofloxacin in milk that were similar to those found in plasma. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children and adolescents below the age of 18 years have not been established. Ofloxacin causes arthropathy (arthrosis) and osteochondrosis in juvenile animals of several species. (See **WARNINGS**.)

ADVERSE REACTIONS: The following is a compilation of the data for ofloxacin based on clinical experience with both the oral and the intravenous formulation. The incidence of drug-related adverse reactions in patients during phase 2 and 3 clinical trials was 11%. Among patients receiving multiple-dose therapy, 4% discontinued ofloxacin due to adverse experiences.

In clinical trials, the following events were considered likely to be drug related in patients receiving multiple doses of ofloxacin: nausea, 3%; insomnia, 3%; headache, 1%; dizziness, 1%; diarrhea, 1%; vomiting, 1%; rash, 1%; pruritus, 1%; external genital pruritus in women, 1%; vaginitis, 1%; and dysuria, 1%.

Local injection site reactions (phlebitis, swelling, erythema) were reported in approximately 2% of patients treated with the 3.63 mg/mL final infusion concentration of intravenous ofloxacin used in the clinical safety trials. The final infusion concentration of intravenous ofloxacin in the commercially available intravenous preparations is 4.0 mg/mL. To date, individuals administered the 4.0 mg/mL concentration of intravenous ofloxacin have demonstrated clinically acceptable rates of local injection site reactions. Due to the small difference in concentration, significant differences in local site reactions are unexpected with the 4.0 mg/mL concentration.

In clinical trials, the most frequently reported adverse events, regardless of relationship to drug, were nausea, 10%; headache, 9%; insomnia, 7%; external genital pruritus in women, 6%; dizziness, 5%; vaginitis, 5%; diarrhea, 4%; and vomiting, 4%.

In clinical trials, the following events, regardless of relationship to drug, occurred in 1% to 3% of patients: abdominal pain and cramps, chest pain, decreased appetite, dry mouth, dyspnea, fatigue, flatulence, gastrointestinal distress, nervousness, pharyngitis, pruritus, pyrexia, rash, sleep disorders, somnolence, trunk pain, vaginal discharge, visual disturbances, and constipation.

Additional events, occurring in clinical trials at a rate of less than 1%, regardless of relationship to drug, were: Body as a whole: asthenia, chills, malaise, extremity pain, pain, epistaxis
Cardiovascular system: cardiac arrest, edema, hypertension, hypotension, palpitations, vasodilation
Gastrointestinal system: dyspepsia
Genitourinary system: burning, irritation, pain and rash of the female genitalia; dysmenorrhea; menorrhagia; metrorrhagia

Musculoskeletal system: arthralgia, myalgia
Nervous system: seizures, anxiety, cognitive change, depression, dream abnormality, euphoria, hallucinations, paresthesia, syncope, vertigo, tremor, confusion
Nutritional/metabolic: thirst, weight loss
Respiratory system: respiratory arrest, cough, rhinorrhea
Skin/hypersensitivity: angioedema, diaphoresis, urticaria, vasculitis
Special senses: decreased hearing acuity, tinnitus, photophobia
Urinary system: dysuria, urinary frequency, urinary retention

The following laboratory abnormalities appeared in $\geq 1.0\%$ of patients receiving multiple doses of ofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying conditions being treated.
Hematopoietic: anemia, leukopenia, leukocytosis, neutropenia, neutrophilia, increased band forms, lymphocytopenia, eosinophilia, lymphocytosis, thrombocytopenia, thrombocytosis, elevated ESR
Hepatic: elevated alkaline phosphatase, elevated AST (SGOT), elevated ALT (SGPT)
Serum chemistry: hyperglycemia, hypoglycemia, elevated creatinine, elevated BUN
Urinary: glucosuria, proteinuria, alkaluria, hyposthenuria, hematuria, pyuria

Additional adverse events, regardless of relationship to drug, reported from marketing experience with quinolones, including ofloxacin:

Clinical: Cardiovascular system: cerebral thrombosis, pulmonary edema
Gastrointestinal system: hepatic dysfunction, including hepatic necrosis, jaundice, hepatitis; hiccup, intestinal perforation, painful oral mucosa, pseudomembranous colitis
Genitourinary system: vaginal candidiasis
Nervous system: psychotic reactions, ataxia, phobia, agitation, restlessness, aggressiveness, manic reaction, possible exacerbation of myasthenia gravis, dysphasia
Respiratory system: dyspnea, bronchospasm
Skin/hypersensitivity: anaphylactic reactions; erythema multiforme/Stevens-Johnson syndrome, erythema nodosum, exfoliative dermatitis, hyperpigmentation, toxic epidermal necrolysis, laryngeal edema, photosensitivity
Special senses: diplopia, nystagmus
Urinary system: polyuria, renal calculi, renal failure, urinary retention, interstitial nephritis (See **WARNINGS AND PRECAUTIONS**.)

Laboratory: Hematopoietic: agranulocytosis, prolongation of prothrombin time

Serum chemistry: acidosis, elevation of serum triglycerides, serum cholesterol, serum potassium

Urinary: albuminuria, candiduria

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

CRYSTALLURIA and CYLINDRURIA HAVE BEEN REPORTED with other quinolones.

Caution: Federal (USA) law prohibits dispensing without prescription.

FLOXIN[®] is a trademark of Ortho Pharmaceutical Corporation.

US Patent No. 4,382,892

ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869-0602



McNEIL PHARMACEUTICAL
SPRING HOUSE, PA 19477-0776

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While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

NAPROSYN® (NAPROXEN) 500 mg tablets

Brief Summary:

Contraindications: Patients who have had allergic reactions to NAPROSYN, ANAPROX or ANAPROX DS or in whom aspirin or other NSAIDs induce the syndrome of asthma, rhinitis, and nasal polyps. Because anaphylactic reactions usually occur in patients with a history of such reactions, question patients for asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy. If such symptoms occur, discontinue the drug. **Warnings:** Serious GI toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** DO NOT GIVE NAPROSYN® (NAPROXEN) CONCOMITANTLY WITH ANAPROX® (NAPROXEN SODIUM) OR ANAPROX® DS (NAPROXEN SODIUM) SINCE THEY BOTH CIRCULATE IN PLASMA AS THE NAPROXEN ANION. Acute interstitial nephritis with hematuria, proteinuria, and nephrotic syndrome has been reported. Patients with impaired renal function, heart failure, liver dysfunction, patients taking diuretics, and the elderly are at greater risk of overt renal decompensation. If this occurs, discontinue the drug. Use with caution and monitor serum creatinine and/or creatinine clearance in patients with significantly impaired renal function. Use caution in patients with baseline creatinine clearance less than 20 mL/minute. Use the lowest effective dose in the elderly or in patients with chronic alcoholic liver disease or cirrhosis. With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. They may progress, remain unchanged, or be transient with continued therapy. Elevations of SGPT or SGOT occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported rarely. If liver disease develops or if systemic manifestations occur (e.g., eosinophilia or rash), discontinue therapy. If steroid dosage is reduced or eliminated during therapy, do so slowly and observe patients closely for adverse effects, including adrenal insufficiency and exacerbation of arthritis symptoms. Determine hemoglobin values periodically for patients with initial values of 10 grams or less who receive long-term therapy. Peripheral edema has been reported. Therefore, use with caution in patients with fluid retention, hypertension or heart failure. The drug's antipyretic and anti-inflammatory activities may reduce fever and inflammation, diminishing their diagnostic value. Conduct ophthalmic studies if any change or disturbance in vision occurs. For patients with restricted sodium intake, note that the suspension contains 8 mg/mL of sodium. **Information for Patients:** Side effects of NSAIDs can cause discomfort and, rarely, there are more serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with patients the potential risks and likely benefits of NSAID treatment, particularly when they are used for less serious conditions where treatment without NSAIDs may be an acceptable alternative. Patients should use caution for activities requiring alertness if they experience drowsiness, dizziness, vertigo or depression during therapy. **Laboratory Tests:** Because serious GI tract ulceration and bleeding can occur without warning symptoms, follow chronically treated patients for signs and symptoms of these and inform them of the importance of this follow-up. **Drug Interactions:** Use caution when giving concomitantly with coumarin-type anticoagulants; a hydantoin, sulfonamide or sulfonylurea; furosemide; lithium; beta-blockers; probenecid; or methotrexate. **Drug/Laboratory Test Interactions:** The drug may decrease platelet aggregation and prolong bleeding time or increase urinary values for 17-ketogenic steroids. Temporarily stop therapy for 72 hours before doing adrenal function tests. The drug may interfere with urinary assays of SHIAA. **Carcinogenesis:** A 2-year rat study showed no evidence of carcinogenicity. **Pregnancy:** Category B. Do not use during pregnancy unless clearly needed. Avoid use during late pregnancy. **Nursing Mothers:** Avoid use in nursing mothers. **Pediatric Use:** Single doses of 2.5-5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are safe in children over 2 years of age. **Adverse Reactions:** In a study, GI reactions were more frequent and severe in rheumatoid arthritis patients on 1500 mg/day than in those on 750 mg/day. In studies in children with juvenile arthritis, rash and prolonged bleeding times were more frequent, GI and CNS reactions about the same, and other reactions less frequent than in adults. Incidence Greater Than 1%; Probable Causal Relationship: GI: The most frequent complaints related to the GI tract: constipation, heartburn, abdominal pain, nausea, dyspepsia, diarrhea, stomatitis. CNS: headache, dizziness, drowsiness, light-headedness, vertigo. Dermatologic: itching (pruritus), skin eruptions, ecchymoses, sweating, purpura. Special Senses: tinnitus, hearing disturbances, visual disturbances. Cardiovascular: edema, dyspnea, palpitations. General: thirst. Incidence Less Than 1%; Probable Causal Relationship: GI: abnormal liver function tests, colitis, GI bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting. Renal: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis. Hematologic: agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia. CNS: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness. Dermatologic: alopecia, photosensitive dermatitis, skin rashes. Special Senses: hearing impairment. Cardiovascular: congestive heart failure. Respiratory: eosinophilic pneumonitis. General: anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever). Causal Relationship Unknown: Hematologic: aplastic anemia, hemolytic anemia. CNS: aseptic meningitis, cognitive dysfunction. Dermatologic: epidermal necrolysis, erythema multiforme, photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa, Stevens-Johnson syndrome, urticaria. GI: non-peptic GI ulceration, ulcerative stomatitis. Cardiovascular: vasculitis. General: angioneurotic edema, hyperglycemia, hypoglycemia. **Overdosage:** May have drowsiness, heartburn, indigestion, nausea, vomiting. A few patients have had seizures. Empty stomach and use usual supportive measures. In animals 0.5 g/kg of activated charcoal reduced plasma levels of naproxen. Call your Federal law prohibits dispensing without prescription. See package insert for full Prescribing Information.

* Incidence of reported reaction 3%-9%.

Where unmarked, incidence less than 3%.

U.S. patent nos. 3,904,682, 3,998,966 and others.

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FOR CHRONIC ARTHRITIS

EXPECT A FAVORABLE SAFETY PROFILE

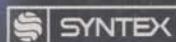
Color-enhanced 3-D CT image of normal
stomach. Supplied by David W.
Stoller, MD, of California
Advanced Imaging.

As with other NSAIDs,
the most frequent complaints
are gastrointestinal, and
rare hepatic and renal reactions
have been reported.

Please see brief summary of prescribing information
on adjacent page.

EXPECT SUCCESS FROM
NAPROSYN[®]
(NAPROXEN) 500 mg tablets

Also available in 375 and 250 mg tablets and in suspension 125 mg/5 mL



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